

The
MEDICAL CLINICS
of
NORTH AMERICA

14

MAYO CLINIC NUMBER

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CONTRIBUTORS TO THIS NUMBER

JOHN E STEVENS, B A , M.D , Fellow in Division of Medicine ²

GEORGE G STILWELL, A B , B M , M D , Consulting Physician in Section on Clinical Pathology ¹

JAN H TILLISCH, A.B , M.D , M S in Medicine, F A C.P , Consulting Physician in Division of Medicine, ¹ Assistant Professor of Medicine. ²

MARVIN M D WILLIAMS, B S , M S , Ph D , Member of Division of Physics and Biophysical Research, Associate Professor of Biophysics ²

¹ In the Mayo Clinic

² On the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota

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SYMPOSIUM ON ANOMALIES OF THE HEART

logic identification of pulmonary stenosis is made more difficult under these circumstances

The clinical picture of the tetralogy of Fallot is usually one which is readily recognized, and accurate diagnosis is possible

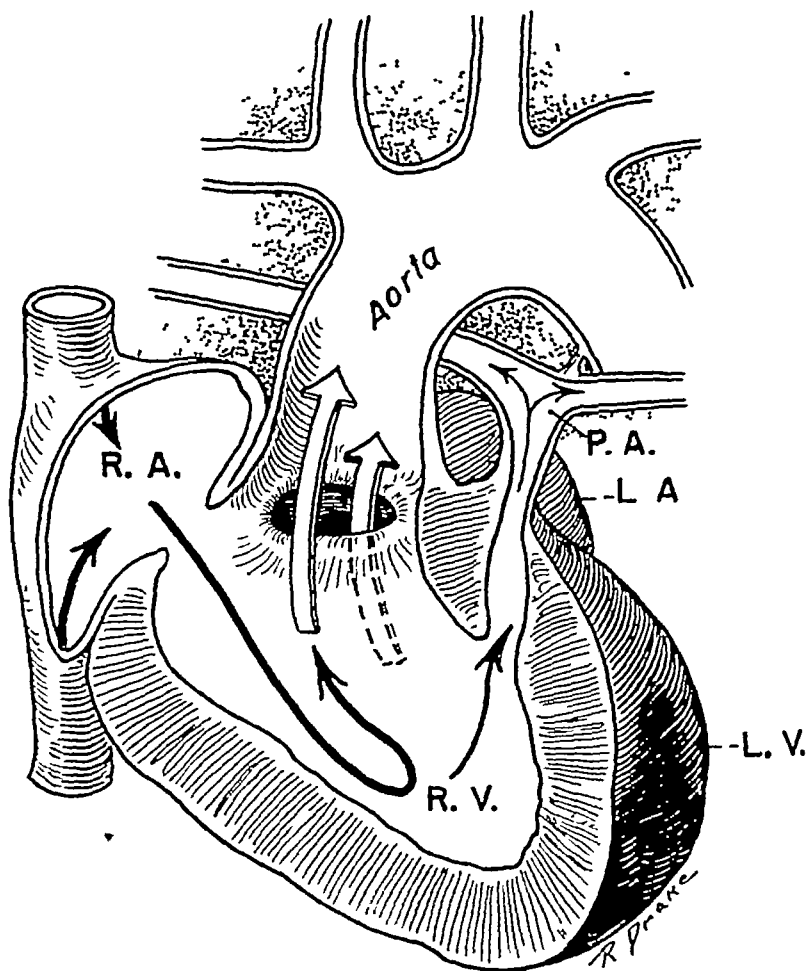


Fig 104 —Tetralogy of Fallot Relationship of aortic orifice to the ventricular septal defect, the small pulmonary artery and narrow subpulmonic channel (Reprinted by permission, from Dry, T J et al. Postgrad Med [In press.])

CLINICAL FEATURES

Cyanosis usually first becomes manifest during the first few months of life probably precipitated by the closure of the ductus and, thus, by the loss of this collateral channel for pulmonary blood flow. When pulmonary atresia exists, patency of the ductus is indispensable and closure of the

exertion a precipitous drop to much lower levels reflects, to a large degree, the severity of the pulmonary stenosis. The use of the modified Millikan oximeter makes these determinations readily available and is of much clinical value in determining the degree of circulatory incapacity.^{4,5} It is surprising that the physical development of these children is seldom retarded in spite of the severe circulatory incapacity.

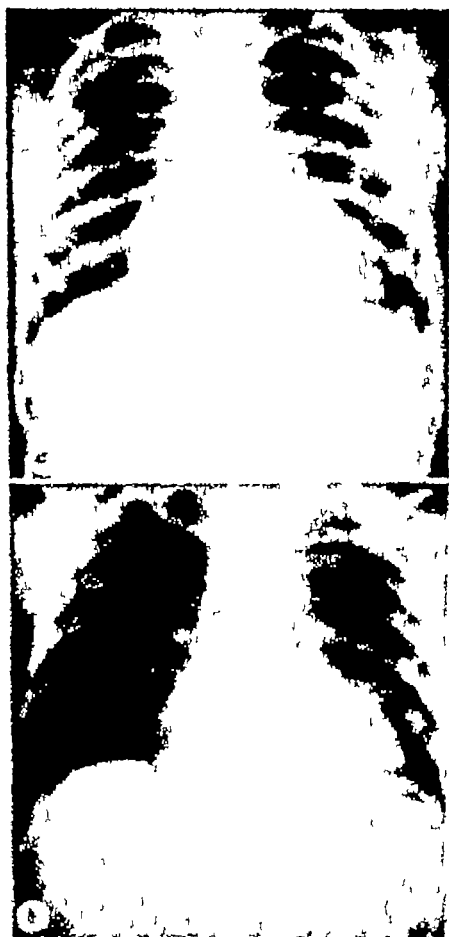
Since the advent of corrective surgery pioneered by the brilliant work of Blalock and Taussig, it has become necessary that physicians fully acquaint themselves with the clinical picture of this particular anomaly. Four cases have been selected for illustration here of certain important variations in the clinical and pathologic picture presented by this congenital cardiac anomaly.

REPORT OF CASES

CASE 1 —Classic tetralogy of Fallot with marked improvement following Blalock-Taussig operation

A male child 3 5 years of age was brought to the Mayo Clinic on March 12, 1947, suffering from attacks of cyanosis and breathlessness. The child was born by cesarean section after a forty-eight hour labor but appeared normal at birth. The mother stated that, although as an infant he seemed pale, his development progressed normally until 10 weeks of age when she noted that he would suddenly become limp and very cyanotic in attacks lasting several minutes. Similar episodes recurred almost daily and were frequently precipitated by feeding. Since the age of 6 months the sudden attacks of cyanosis and syncope had become less frequent but breathlessness and cyanosis on moderate exertion were noted. At 3 years of age the child could walk only a few steps without assuming the usual squatting posture to rest, and there was persistent cyanosis of the face, lips and fingers.

On examination the child appeared well developed. There was moderate cyanosis of the face with suffusion of the conjunctiva, mulberry-like discoloration of the tongue and slight clubbing of the fingers and toes. The heart was not enlarged. On auscultation a coarse, systolic murmur was heard over the entire precordium, loudest at the base. The hemoglobin measured 18.1 gm per 100 cc of blood and the hematocrit reading was 65 per cent erythrocytes. Roentgenograms of the chest and roentgenoscopic examination of the heart revealed the heart to be of normal size but there was the typical concavity in the region of the pulmonary conus indicative of pulmonary stenosis (fig 105, see a). There was absence of pulsa-



tions in the hilar vessels. The aortic arch was in its normal position on the left. The electrocardiogram revealed sinus rhythm with marked right axis deviation (fig 106). The arterial hemoglobin oxygen

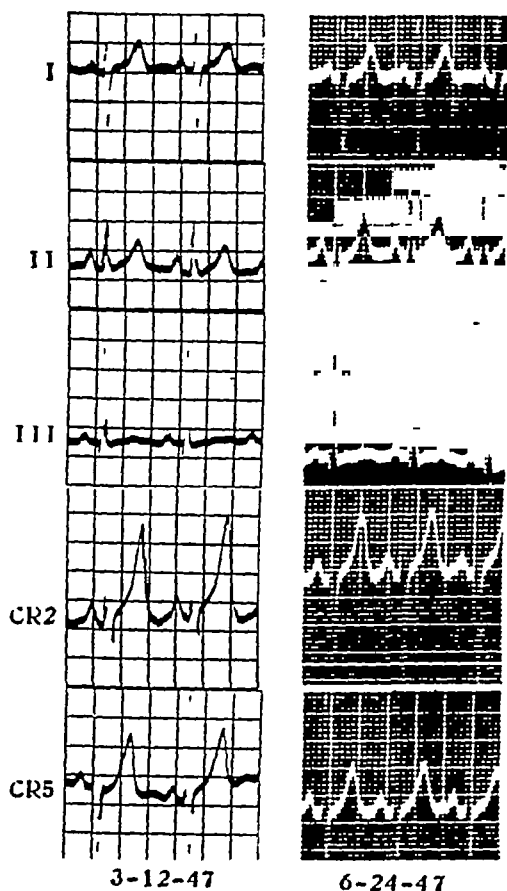


Fig 106 (Case 1) —Electrocardiograms before and three months after operation show right axis deviation and large biphasic QRS complexes in precordial leads with no change in pattern after Blalock-Taussig operation

saturation was 53 per cent (normal 95 per cent). A graphic illustration of the change in oxygen saturation associated with exertion as measured by the modified Millikan oximeter is illustrated in figure 107.

A diagnosis of tetralogy of Fallot was made and surgical treatment was recommended. On April 1, 1947, an end-to-side anastomosis of the left subclavian artery with the left pulmonary artery was made by Dr O T Clagett. After the operation a continuous arteriovenous fistula type of murmur could be heard over the left anterior and posterior portions of the thorax. There was a marked decrease in the intensity of the cyanosis. Convalescence was essentially

purpose in mind and that is to overcome the deficiency in the blood flow in the pulmonary artery, thus, operation is not indicated in those lesions in which there is already adequate pulmonary circulation

In the selection of patients for surgical treatment one must consider the following questions 1 Is the lesion one in which there is a limited flow of blood to the lungs? This information can best be obtained by roentgenoscopic examination, and the indications of reduced pulmonary blood flow have been discussed under the clinical features of tetralogy In cases in which there is uncertainty regarding this point, cardiac catheterization may give valuable aid 2 Is the level of arterial oxygen saturation sufficiently low that the blood would be capable of picking up more oxygen if a portion of the arterial blood was shunted into the lungs? Patients with a resting oxygen saturation of 80 to 85 per cent will not be benefited by this type of operation unless the level of saturation drops markedly with minimal exertion 3 Are the pressure relationships between the pulmonary artery and aorta or systemic vessel such that blood flow from the arterial to the pulmonary vessel will take place in the created anastomosis? Pulmonary stenosis and tricuspid atresia always will be associated with reduced pressure in the pulmonary artery In cases of Eisenmenger's complex, in complete transposition of the great vessels and in single ventricle with rudimentary aorta, the pressure relationships will not favor a functioning anastomosis 4 Can the heart accommodate to the establishment of the new anastomosis? Cardiac malformations associated with intense cyanosis but with cardiac enlargement usually indicate a more serious derangement than pulmonary stenosis of the tetralogy type, and the margin of safety in accommodation to the creation of an artificial ductus is greatly reduced in such cases

Inasmuch as the intracardiac defects are not affected by the creation of an artificial ductus, the question has often been raised as to whether there is an actual increase in the cardiac load after the creation of the anastomosis In answer to this question, we must consider first the part each ventricle plays in the work load of the heart prior to the anastomosis In

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tetralogy of Fallot the right ventricle is not only responsible for the propulsion of the blood through the narrowed pulmonary channel to the lungs but, because of the presence of the ventricular septal defect with aortic overriding, this ventricle also is carrying a considerable load of the systemic circulation as well. We might assume then that the right ventricular pressure would be considerably higher if the septum were intact and all blood from the right ventricle were forced through the narrowed channel of the pulmonary stenosis. Such a condition, of course, exists in pure pulmonary stenosis. In tetralogy, however, the right ventricular pressure can increase only sufficiently to equal that required for the systemic circulation. Thus, I believe, gives an explanation as to why the right ventricle does not enlarge in tetralogy more than it does and why, in view of the decreased total load on the left ventricle, the heart as a whole is seldom enlarged. With the creation of an artificial ductus, a greater portion of the blood will then be returning through the pulmonary circuit to the left side of the heart and the left ventricle then assumes a significant role in maintaining the pulmonary circulation. This would indicate that there is an equalization of work load upon both ventricles after operation whereas with the relief of the severe anoxic state the demand on the heart for systemic circulation is consequently decreased. From this analysis, one may well assume that after the creation of the anastomosis there will be a relatively increased load upon the left ventricle in comparison with the preoperative load. This concept has so far been borne out clinically. The left ventricle may show transient dilatation after operation but as it becomes adapted to its increased load the heart tends to resume its preoperative size and there is an increase in the pulmonary vascular markings on roentgenologic examination, denoting an increase in the pulmonary blood flow.

CASE 2 — Tetralogy of Fallot with severe attacks of anoxia and fatal termination. Postmortem findings illustrated

♂ A male child 3 years of age was admitted to the Clinic on October 28, 1947. Birth and development for the first 9 months of life were

considered to be normal. At 9 months of age the child first experienced a sudden episode of syncope with cyanosis. A diagnosis of congenital heart disease was made by the family physician. Since this first attack of cyanosis with syncope, similar attacks associated with rigidity and dyspnea recurred almost daily without warning, lasting as long as fifteen minutes. The child otherwise continued to develop normally but seemed to tire easily. During the intervals

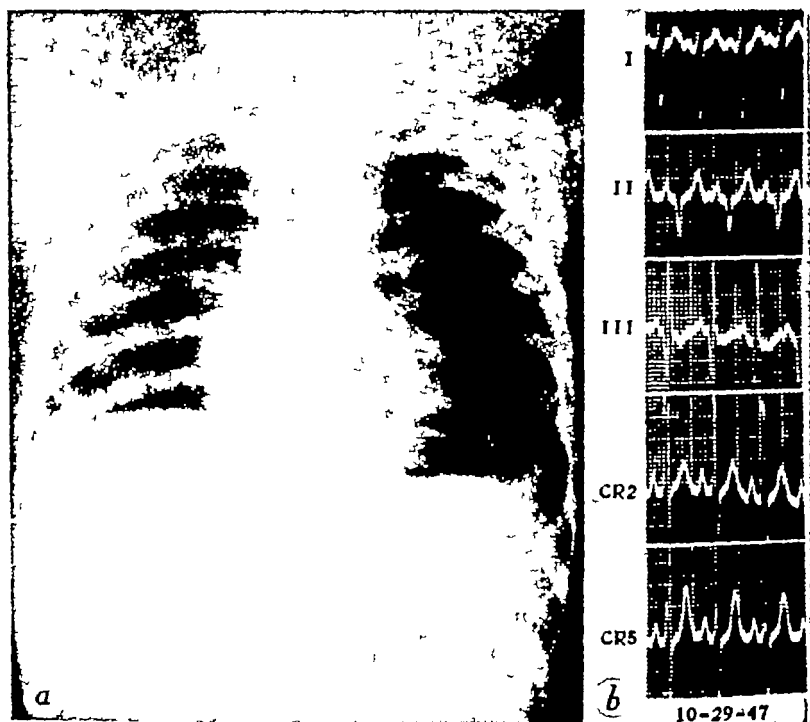


Fig 108 (Case 2) —*a*, The heart is not enlarged. It has the characteristic "tetralogy contour." The vascular markings at the hilus are quite prominent but on roentgenoscopic examination, pulsations in these vessels were absent. *b*, Marked right axis deviation.

between attacks only minimal cyanosis, intensified by cold and exertion, was noted. On physical examination the child seemed alert, active and intelligent, and development was normal. There was moderate cyanosis of the face, lips, fingers and toes, with minimal clubbing. There was a systolic murmur with palpable thrill, maximal at the left sternal border in the fourth interspace. Roentgenograms of the thorax (fig 108*a*) and roentgenoscopic examination revealed the heart to be of normal size with concavity in the region normally occupied by the pulmonary conus and absence of pulsations in the pulmonary hilar shadows. The electrocardiogram revealed marked right axis deviation (Fig 108*b*). The hemoglobin measured 17.9 gm.

The erythrocytes numbered 5 480,000 per cubic millimeter of blood. A diagnosis of pulmonary stenosis, tetralogy of Fallot type was made. On the morning following the preliminary examination the child became listless, weak and dyspneic, with marked intensification of the cyanosis. The mother stated that his appearance was similar to that noted in previous attacks but instead of being transitory the state continued. Van Slyke analyses as well as oximeter



Fig. 109 (Case 2) —Right ventricle of the heart has been opened showing all the anatomic features in tetralogy of Fallot namely (1) narrowed subpulmonic channel (2) dextroposition of the aortic orifice in relation to (3) the large defect in the ventricular septum and (4) thickened right ventricular wall.

readings on a sample of arterial blood revealed an arterial oxygen saturation of only 13 per cent (normal 95 per cent). The child was immediately hospitalized, placed in an oxygen tent but failed to respond. Progressive terminal pneumonia developed and he died forty-eight hours after admission to the hospital.

On postmortem examination the classic anatomic features of tetralogy of Fallot were found. The anterior wall of the heart was formed almost in its entirety by the right ventricle and the apex of the heart was raised 1.5 cm. above the diaphragm. The pulmonary artery was narrow and almost obscured by the ascending aorta.

The foramen ovale was found to be closed. There was a defect in the membranous portion of the ventricular septum measuring 0.8 by 0.5 cm and the aortic orifice straddled this septal defect in such a manner that approximately two thirds of it was associated with the right ventricle and one third with the left ventricle (fig 109). The right ventricular wall was thick, measuring 0.6 to 1.0 cm, as compared to the left ventricular wall which measured 0.5 to 0.6 cm.



Fig 110 (Case 2) —Posterior view of the lungs showing the enlarged collateral bronchial arteries entering the hilum of the lungs

Beneath the opening of the pulmonary artery was a slitlike channel commonly called a "third ventricle." This channel extended for a distance of 1.9 cm below the pulmonary valve and measured only 1 mm in diameter at its narrowest point. The pulmonary valve was bicuspid, being composed of an anterior and a posterior leaflet only. The pulmonary artery was narrowed, measuring 0.6 cm in diameter, as compared to the aorta which measured 1.9 cm in diameter. The ductus arteriosus was closed. The first left intercostal artery was unusually large and gave rise to right and left collateral bronchial artery branches which were seen to enter the lung at the hilum (fig 110).

Comment—The anatomic derangements in tetralogy of Fallot are well illustrated in this case and the subpulmonic third ventricle channel is clearly shown.

This child died primarily of severe anoxemia, the pneumonic process being a terminal phenomenon. This raises the question of the etiology of the severe transitory anoxemia that is noted so frequently in these children especially during the early years of life and that as this case so well demonstrates, may result in death during an attack. The flow of blood through the narrowed pulmonary opening is, in all probability governed principally by the pressure in the right ventricle which, in turn, owing to the direct association through the septal defect and aorta, is a reflection of resistance in the systemic circuit. The attacks of severe cyanosis probably result from a sudden change in the partitioning of the right ventricular blood between the pulmonary and systemic circulations. Although factual data are lacking regarding this concept, it would seem most likely that with certain levels of anoxemia, which may vary in different individuals, there is a sudden loss of vasomotor tone. The pressure in the systemic circulation falls the ventricular pressure drops and the right ventricular blood finds still an easier outlet to the systemic circulation than through the narrowed pulmonary orifice the result being a further reduction in pulmonary flow and an increase in the amount of venous blood entering the systemic circulation, during which time there is a pronounced increase in the severity of the anoxemia. A return of systemic vascular tone brings again a greater degree of partitioning of blood into the pulmonary circulation and the sudden severe anoxemia lessens as larger amounts of blood are aerated.

Even though these attacks seem to occur less frequently as the child becomes older and better adjusted to a state of chronic anoxemia or because collateral channels through the bronchial arteries allow a greater volume of pulmonary circulation, the child showing an increasing frequency and severity of these attacks should be considered in serious difficulty and early operation should be advised. In consideration of the fact that it was not possible to be of help in the case presented here, even with the patient receiving constant inhalations of oxygen, it would seem unlikely that he could have withstood operation during this final attack. It seems regrettable that operation could not have been performed.

formed prior to this final attack, for then it might well have been a lifesaving procedure

CASE 3 — Tetralogy of Fallot with moderate pulmonary stenosis and minimal incapacity

A female, 24 years of age, came to the Clinic in October, 1947. Her primary object in seeking consultation at that time was to determine whether or not she could be allowed to undertake the risk of pregnancy. The patient was told she had been a "blue baby" at birth. Cyanosis had persisted throughout childhood and she had never been able to be as active as other children because of easy fatigability, and the cyanosis had become progressively more intense. From the age of 13 to 17 years the patient could walk only one or two blocks without experiencing marked fatigue. Subsequently, however, she had noted an increase in her exertion tolerance and, at the time she came to the Clinic, was able to attend dances and to carry out her usual activities in caring for her home.

Physical examination revealed a young woman of small stature but well developed, weighing 106 pounds (48 kg). Her blood pressure was normal. She appeared very cyanotic, with suffusion of the conjunctiva and deep purplish cyanosis of the tongue, mucous membranes and retinas, and there was marked engorgement of the retinal vessels. There was pronounced clubbing of the fingers and toes. The face and nail beds were deeply cyanotic. There was no evidence of pulmonary congestion. The heart tones were clear and there was a high-pitched systolic murmur along the left border of the sternum, maximal in the left third interspace. Polycythemia was intense, with a hemoglobin value of 24.8 gm. and an erythrocyte count of 7,420,000, the hematocrit reading was 85 per cent erythrocytes. The electrocardiogram revealed right axis deviation, with large biphasic QRS complexes in the precordial leads. Roentgenograms of the thorax revealed the typical cardiac contour seen in tetralogy of Fallot (fig 111). With the patient at rest the value for arterial hemoglobin oxygen saturation was 76.4 volumes per cent and with the standard exercise test of walking on the treadmill at a rate of 1.7 miles per hour for five minutes the value for arterial oxygen saturation dropped to 68.8 per cent. With the inhalation of 100 per cent oxygen there was a rise in the level of oxygen saturation to 85.7 per cent.

A clinical diagnosis of pulmonary stenosis of the tetralogy of Fallot type was made. It was thought that pregnancy would be hazardous and, therefore, the patient was advised against it.

Comment — This case is reported to illustrate the point that in some instances patients with tetralogy of Fallot are not

greatly disabled and that an occasional patient may live for many years. The average duration of life in the cases of pulmonary stenosis associated with ventricular septal defect, as recorded in Maude Abbott's series of cases, was 12 years. This defect, however, is still the most common anomaly found in adults with congenital heart disease associated with per-

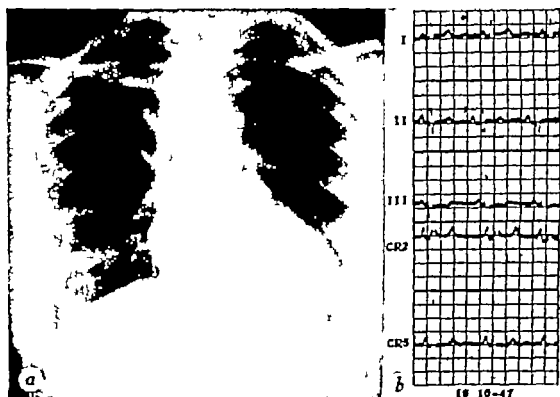


Fig 111 (Case 3) —Tetralogy of Fallot in a woman 24 years of age *a* Roentgenogram; *b* electrocardiogram

sistent cyanosis, and instances of unusually long duration of life are on record. The most notable example is the man reported on by White and Sprague who survived to his sixtieth year.

The level of disability may vary greatly, depending largely on the severity of the pulmonary stenosis and the consequent level of anoxemia. It is of interest to note that in this case the degree of disability was greater during the period of adolescence than after the patient reached maturity. The increased demand on the circulation associated with the period of rapid growth in all probability is responsible for this manifestation. One must also bear in mind the role played by the development of collateral circulation to the lungs in maintaining a higher level of arterial oxygen saturation. The find-

ing of compensatory collateral channels to the lungs by way of the bronchial arteries, the intercostals, phrenic and esophageal vessels is noted more commonly in older patients with pulmonary stenosis

At what level of arterial oxygen unsaturation the stimulus to the development of polycythemia occurs in these cases has not been definitely established. In the absence of polycythemia, an arterial oxygen saturation value of 85 per cent is not ordinarily associated with visible cyanosis, yet when polycythemia occurs, cyanosis may be marked even at this relatively high level of arterial oxygen saturation. A patient with pulmonary stenosis but with fully developed collateral circulation to the lungs may notice little disability at this level of oxygen saturation, provided it does not drop significantly with moderate exertion. The degree of polycythemia itself, although forming an increased hazard to life because of the tendency to vascular thrombosis, does not seem to play a significant role in the degree of incapacity to physical exertion, even when the hematocrit readings may be as high as 70 to 80 per cent erythrocytes

CASE 4 —Pulmonary stenosis without ventricular septal defect but with patent foramen ovale. Death from cerebral abscess

A farmer, 26 years of age, was admitted to the hospital on November 28, 1947, because of cerebral complications, with left hemiplegia. A diagnosis of congenital heart disease had been made at the age of 3 years by the family physician when the mother sought consultation because she had noted periodic mild cyanosis of the child's lips and undue breathlessness on exertion. By the time the patient was 16 years old, cyanosis had become persistent and clubbing of the fingers had developed, yet he was only moderately limited in his capacity for physical exertion and continued to do most of the farm chores without difficulty. In April, 1947, seven months prior to his admission, he had been injured in an auto accident but apparently sustained no head injury. On November 16, 1947, on awakening in the morning he had three generalized convulsive seizures each preceded by short periods of spasmodic jerking of the head to the left prior to loss of consciousness. Two days later left hemiplegia developed.

Preliminary examination revealed a well-developed young man with marked cyanosis and clubbing of the fingers and toes. There was complete left hemiplegia. Cardiac examination revealed a loud systolic murmur, with a thrill that was maximal in the left third

and fourth interspaces. The blood pressure was normal. The hemoglobin measured 24.8 gm, the erythrocyte count was 7,850,000 and the hematocrit reading was 80 per cent erythrocytes. Roentgenograms of the head were normal. Roentgenograms of the thorax and roentgenoscopic examination of the heart (fig. 112a) revealed moder-

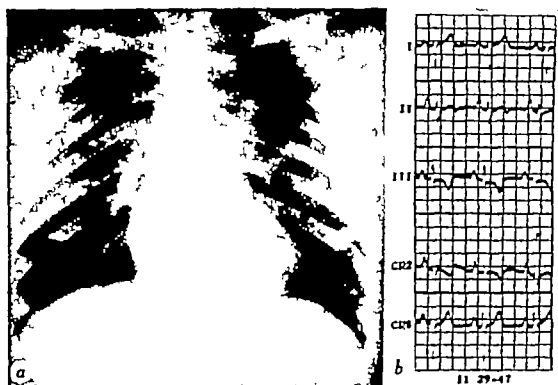


Fig. 112 (Case 4)—a Valvular stenosis of the pulmonary artery with intact ventricular septum. Prominence of pulmonary conus and pulmonary artery shadows. b right axis deviation and marked right ventricular strain pattern.

ate right ventricular enlargement with prominence of the pulmonary conus shadow. The pulmonary artery shadows were prominent but pulsations in these vessels were feeble. The electrocardiogram (fig. 112b) revealed sinus rhythm with marked right axis deviation, inversion of the T waves in leads II and III and exaggeration of the P waves in leads II and III. The precordial lead CR₄ revealed an inverted T wave with high voltage R wave. Examination of the ocular fundi revealed moderate cyanosis of the retinas. There appeared to be mild chronic edema of the disks which was interpreted to be due to venous stasis and cyanosis and not secondary to increased intracranial pressure. The electro-encephalogram revealed moderate right temporal delta localization. The value for arterial hemoglobin oxygen saturation at rest was 84.6 per cent. Blood cultures gave negative results.

A diagnosis of congenital heart disease, probably Eisenmenger complex, marked secondary polycythemia with cerebral vascular thrombosis and hemiplegia, was made.

Phlebotomy was performed repeatedly, a high intake of fluids, being maintained in the hope of preventing further vascular t

bosis On December 13, a severe right frontal headache with vomiting developed There was an increase of the paresis in the left extremities and drowsiness occurred Twenty-four hours later there was a marked slowing of the heart rate to 48 beats per minute, and he became more stuporous, still complaining of severe right frontal headache His course had remained afebrile In view of these findings of progressive increased intracranial pressure, a right fronto-temporal craniotomy was carried out under local infiltration anesthesia No abscess, tumor or subdural hematoma was disclosed and it was assumed therefore, that the cerebral lesion was that of



Fig 113 (Case 4)—View of pulmonary artery from above which shows the cone-shaped diaphragm formed by a fusion of the pulmonary leaflets and producing marked obstruction of the pulmonary orifice The opening in the center measured only 0.5 cm The pulmonary artery was of normal size

cerebral vascular thrombosis His condition remained essentially unchanged for the next two weeks, then progressive somnambulance, stupor and finally coma began to develop, and the patient died on December 31, 1947

Postmortem examination revealed enlargement of the heart, which weighed 425 gm The pulmonary artery arose exclusively from the right ventricle The pulmonary valve was the site of congenital stenosis The valve was guarded by a diaphragm-like cone-shaped membrane in the center of which there was an opening which measured 5 mm in diameter (fig 113) The diameter of the pulmonary artery at this level measured 2 cm The diaphragm-like membrane forming the pulmonary valve was, in essence, a fusion of the 3 pulmonary leaflets There was a considerable degree of hypertrophy of the right ventricular wall which measured 1.1 cm in average thickness The outlet of the right ventricle was considerably nar-

rowed and measured less than 0.5 cm. in diameter. The ventricular septum was intact. The aorta rose exclusively from the left ventricle, the wall of which measured 1.5 cm. in thickness. The great veins drained into their appropriate atria. The right atrium was slightly dilated and there was a patent foramen ovale measuring 1.5 by 0.5 cm. (fig. 114). There was no evidence of bacterial endocarditis.



Fig. 114 (Case 4) —Left atrium and atrial septum with patent foramen ovale.

In the upper aspect of the left pulmonary artery just beyond the bifurcation and in line with the outflow tract of the right ventricle there was an intimal patch measuring 2.0 by 1.0 cm. which was characterized by roughening and slight elevation of the intimal surface. There were 2 prominent bronchial arteries. The right arose from the second right intercostal artery. The left bronchial artery arose from the fourth right aortic intercostal. The brain contained a large abscess which measured 6 cm. in diameter and involved the right frontal lobe (fig. 115). The wall of the abscess was relatively thick and firm, and the surrounding cerebral tissue was soft and edematous. A culture from the abscess revealed anaerobic diphtheroids.

Comment —This case is of unusual interest not only because of the finding of pulmonary stenosis with intact ventricular

septum but also because it illustrates the predisposition of individuals with congenital heart disease to the development of cerebral abscess



Fig 115 (Case 1) —Cerebral abscess in the right frontal lobe

The clinical diagnosis was in error in this case, the presence of pulmonary stenosis not being suspected. Yet, in retrospect, the clinical findings become understandable in the light of the findings at autopsy. The late development of cyanosis, the relatively high level of resting arterial oxygen saturation and the minimal physical disability from the cardiac lesion all seem to indicate a relatively good pulmonary circulation, and the prominence of the pulmonary conus shadow seen on the roentgenogram seemed sufficient to exclude the presence of pulmonary stenosis. The intensity of the cyanosis in this case was thought to be more a reflection of the polycythemia than

an indication of severe oxygen unsaturation of the arterial blood. These findings suggested the presence of a ventricular septal defect with aortic overriding but without pulmonary stenosis, the syndrome commonly termed "Eisenmenger's complex."

Two findings were not given sufficient clinical emphasis in the evaluation of this case and, had they been, the correct diagnosis might have been suspected. I refer first, to the roentgenoscopist's report of only minimal pulsation in the pulmonary artery shadows, even though these shadows were prominent, and, second, to the finding of a marked right ventricular strain pattern on electrocardiographic examination. The absence of normal pulsations in the pulmonary artery shadows should have indicated, in the presence of a pulmonary artery of normal or increased size, a valvular type of pulmonary stenosis. The pulmonary stenosis in this case might have been more clearly and diagnostically demonstrated had the patient's condition allowed cardiac catheterization. Catheterization of the pulmonary artery would have revealed a greatly reduced pressure in the pulmonary artery distal to the stenosis. Although the electrocardiogram in Eisenmenger's complex usually shows right axis deviation, one does not find the pattern of right ventricular strain with T wave negativity in leads II and III and ST segment changes as is found in those conditions that produce isolated strain on the right ventricle.

Complete pulmonary stenosis without ventricular septal defect is a rare lesion. Although my colleagues and I have made the diagnosis clinically by means of cardiac catheterization in an acyanotic young woman of 30 years of age, the only autopsy specimen we have of this type of defect in our collection of 133 examples of major cardiac anomalies is the one in case 1. In approximately half of the cases of pulmonary stenosis without ventricular defect reported in the literature¹³ the foramen ovale has remained patent, allowing, under conditions of increased pressure in the right side of the heart, blood from the right auricle to enter the arterial circulation. The venous arterial shunt through the auricles tends to simulate functionally the circulation in tetralogy of Fallot.

except that the left ventricle is alone responsible for the systemic circulation. When both auricular and ventricular septa are intact the lesion becomes one of pure pulmonary stenosis and all of the blood returning to the right side of the heart has to be forced through the narrow valvular stenosed part and through the pulmonary circuit. Under such circumstances cyanosis usually does not develop until adolescence or adult life is reached and then only as a manifestation of incapacity of the right ventricle to maintain the pulmonary circulation, with consequent right heart failure.

The most common cerebral complication in the course of cyanotic congenital heart disease with secondary polycythemia is cerebral thrombosis. The extremely high blood viscosity with hematocrit readings of 80 to 85 per cent is not uncommon and, thus, intravascular thrombosis is a serious hazard. Cerebral abscess is also a common complication in any type of congenital heart disease in which there is a venous arterial shunt, and the records of the Clinic now show 6 cases of cerebral abscess in association with various septal defects. The cerebral symptoms due to abscess may develop insidiously or very abruptly, as was true in this case, and may simulate closely the clinical findings in acute cerebral vascular occlusion.

SUMMARY

Four cases of pulmonary stenosis have been reported, the first 2 cases occurred in children 3 years of age and illustrate the typical clinical features of pulmonary stenosis of the tetralogy of Fallot type. The first child obtained a very successful result from the operation of a Blalock-Taussig anastomosis, the second child died of anoxemia. Transient episodes of severe anoxemia with loss of consciousness was the prominent clinical feature in the second case and preceded the terminal attack. The usual anatomic changes found in tetralogy of Fallot are also well illustrated in this case. The third case illustrates the adaptability of the circulation when the degree of stenosis is not severe, and the fourth case of pulmonary stenosis without ventricular septal defect has been reported because of the rarity of this lesion and because of the interesting complication of cerebral abscess.

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CLINICAL-PATHOLOGIC CORRELATION OF SOME LESS COMMON CYANOTIC CONGENITAL CARDIAC DEFECTS IN INFANTS

JAMES W DUSHANE

ACCURATE diagnosis of the specific anatomic lesions in congenital heart disease is difficult in early infancy. Multiple defects often exist in a single heart and, frequently, the additional defects may compensate for one abnormality by improving the function of the heart and permitting more adequate circulation of the blood. A functional diagnosis can be made, in many cases of congenital heart disease, by understanding the altered physiology of the circulation and recognizing the clinical manifestations of these changes. Correlation of the clinical findings with the results of detailed study of the pathologic specimens in infants with congenital malformations of the heart and great vessels, as so brilliantly advocated for many years by the late Dr. Maude Abbott and emphasized more recently by Dr. Helen Taussig in her excellent book,⁸ has increased immeasurably our knowledge of the altered physiology. Until recently the exact differentiation of one anatomic anomaly from another was mostly of academic interest and of no practical importance, but, since the advent of successful surgical treatment of a few types of congenital disorders, renewed interest in this field has been stimulated.

Understanding of the events that occur in orderly progression in the embryologic development of the normal human heart is essential for the study of the various abnormalities that may occur as a result of arrest or errors in the development of the cardiovascular system. No attempt will be made here to review details of the development of the heart in the fetus or to analyze the various theories explaining the malformations in the pathologic specimens. It is well to remember that the primitive cardiac tube in the three week old embryo evolves into the complete complicated adult structure by the eighth week of fetal life. During this brief span of five weeks there occurs the bending, looping, rotating and torsion of the cardiac tube to produce the four chambers with their

respective valves and intracardiac septa. An arrest in development or an error in the normal progress of this intricate differentiation of tissue can result in serious defects in anatomy and function of the heart. Reports of 4 cases are presented herein to illustrate some of the less common cardiac malformations which are usually incompatible with extra-uterine life for more than a few months.

REPORTS OF CASES

CASE 1 — *Atresia of the mitral valve with rudimentary left ventricle, patent foramen ovale and ventricular septal defect* (This case was reported elsewhere ³)

A white male infant was born at full term on March 24, 1946, after a normal pregnancy during which there was no known infection. The birth weight was 3,850 gm (8 pounds, 8 ounces). The newborn infant appeared normal and his color was good. On the sixth day of life a precordial systolic murmur was noticed. Roentgenologic examination revealed marked cardiac enlargement and apparent pulmonary congestion. The electrocardiogram made at that time revealed sinus tachycardia and slight right axis deviation. At the age of 2 months the baby was re-examined because of his failure to gain weight. The mother had noticed no cyanosis but the examining physician pointed out that the infant's lips were dusky when he was lying on his abdomen. A systolic murmur was described which was loudest at the left of the sternum. There was no evidence of cardiac failure although the heart was enlarged.

The infant did not make a satisfactory gain in weight and was admitted to the hospital on June 27, 1946, at the age of 3 months. At that time he appeared poorly nourished but there was no cyanosis. The systolic heart murmur remained unchanged. On roentgenologic examination, the heart was greatly enlarged and the cardiac contour indicated right ventricular and right auricular enlargement (fig 116a). The electrocardiogram at that time showed a low amplitude T wave in lead I and exaggerated P waves in leads II and III in addition to right axis deviation (fig 116b). The erythrocyte count was 3,880,000 per cubic millimeter and there were 13.5 gm of hemoglobin per 100 cc of blood. The leukocytes numbered 13,000 per cubic millimeter. In the hospital the baby failed to gain weight, and a fever developed on the thirteenth day which gradually increased to 106° F by the twenty-ninth day in spite of penicillin therapy. Blood culture gave negative results. During this time some dyspnea and cyanosis appeared. On the twenty-ninth day the baby became markedly cyanotic and dyspneic and died three days later, at the age of 4 months.

At autopsy the primary lesion of the heart was atresia of the orifice of the mitral valve. There was no opening between the left atrium and the left ventricle, only a dimple was evident at the expected location of the mitral valve (fig 116c). The foramen ovale was patent with the valve lying to the right of the plane of the

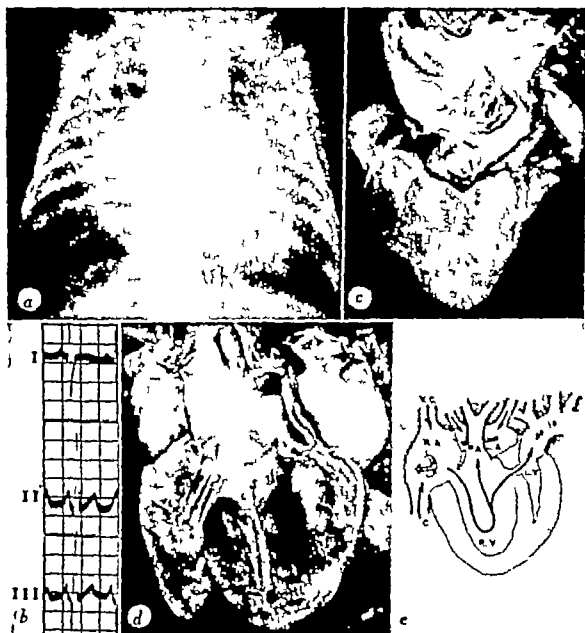


Fig 116 (Case 1)—a Cardiac enlargement is evident. Bronchovascular shadows are prominent. b Patient 3 months old. The P waves are exaggerated in leads II and III. There is right axis deviation. c, The left atrium has been opened to show the patent foramen ovale and absence of the mitral orifice and valve. There is a small dimple at the expected site of the mitral orifice. d, The right ventricle is displayed below. The pulmonary artery is shown arising from the right ventricle and dividing into its right and left branches. The opened aorta is seen in the upper right portion of the photograph; this vessel arches over the left pulmonary artery. e, Course of the blood flow through the heart. (Reprinted by permission from Edwards J. E. and Rogers H. M. Atresia of the orifice of the mitral valve: report of a case. *Bull. Internat. Soc. M. Muséum*, 27-62-76, 1917.)

interatrial septum, as though the valve had been forced from its normal position at the left of the septum through the foramen ovale. The right atrium was greatly dilated and communicated with the right ventricle through the tricuspid orifice which was wide, measuring 5 cm in circumference. The right ventricle was large, constituting most of the ventricular portion of the heart (fig 116d). There was a defect in the upper part of the ventricular septum measuring 3 by 6 mm. Through this defect the right ventricle communicated with a small, rudimentary left ventricle which had no papillary muscles. The aorta arose from the small left ventricle and arched over the left pulmonary artery rather than over the right as in the normal person (fig 116d). The ductus arteriosus was closed.

Comment—This heart represents an example of a functioning single ventricle. During fetal life the blood from the pulmonary veins emptied into the left atrium but the mitral valve was closed, so the only outlet was through the foramen ovale into the right atrium. Thus the normal right to left blood flow through the foramen ovale was reversed. The entire venous return from the pulmonary circuit entered the right atrium where it joined the venous return from the systemic circulation and passed through the tricuspid orifice into the right ventricle. The major portion of the blood left the large ventricle via the pulmonary artery, some entering the pulmonary circuit and the rest traversing the ductus arteriosus to the aorta. A small part of the right ventricular blood was shunted through the ventricular septal defect into the left ventricle and out into the aorta. The right ventricle constituted the systemic ventricle and carried out its usual role of supplying the pulmonary circulation as well. Since the entire volume of blood of the fetus entered the right atrium and ventricle, this increased load caused dilatation and hypertrophy of these chambers. The incomplete ventricular septum was pushed to the left owing to widening of the right ventricle, and the left ventricle remained rudimentary, actually constituting only an outlet passage to the aorta. Usually, a small left ventricle is associated with a hypoplastic aorta because of the deficient blood flow through that vessel, but in this heart, the aorta was of normal caliber.

At birth the heart was enlarged as a result of the strain placed on the right atrium and ventricle in fetal life. As the

ductus arteriosus closed, the systemic circulation was supported by the small amount of blood passing through the ventricular septal defect to the aorta. The pulmonary system received the large portion of blood from the dominant right ventricle (fig 116e). As a consequence, more oxygenated blood than systemic venous blood returned to the heart, and the lack of cyanosis, except as a terminal phenomenon, in this patient is readily explainable. The apparent pulmonary congestion, as demonstrated by roentgenogram, is likewise accounted for by the increased pulmonary blood flow. The inadequate systemic circulation, produced by closure of the ductus arteriosus, presumably was responsible for the failure of normal development of this infant after birth. It is evident, from the review of the pathology, that proper diagnosis should have been suspected during life, because all of the clinical findings pointed toward a functionally single ventricle with good pulmonary circulation. The location and character of the systolic murmur in this case, was of no diagnostic importance because a similar murmur may occur in other types of congenital cardiac defects.

Speculation concerning possible surgical correction of the altered physiology in mitral atresia is not very hopeful. An anastomosis between the pulmonary artery and the aorta, as devised by Potts, Smith and Gibson for patients with tetralogy of Fallot, might increase the systemic blood flow if pressure relationships in these two vessels were favorable but there would be no assurance that such a shunt would function.

CASE 2—Aortic atresia with intact ventricular septum, patent foramen orale and patent ductus arteriosus

A white female infant was born April 15, 1947, at full term, the result of the first pregnancy of young healthy parents. The birth weight was 3,480 gm (7 pounds 9 ounces). There was no cyanosis at birth. At the age of 15 days, some blueness of the lips was noted with crying. These cyanotic spells increased in severity and frequency, and the baby failed to gain weight. She was admitted to the hospital on July 15, 1947, at the age of 3 months. Physical examination revealed a small, undernourished infant with constant cyanosis which became severe with crying. There was a systolic murmur at

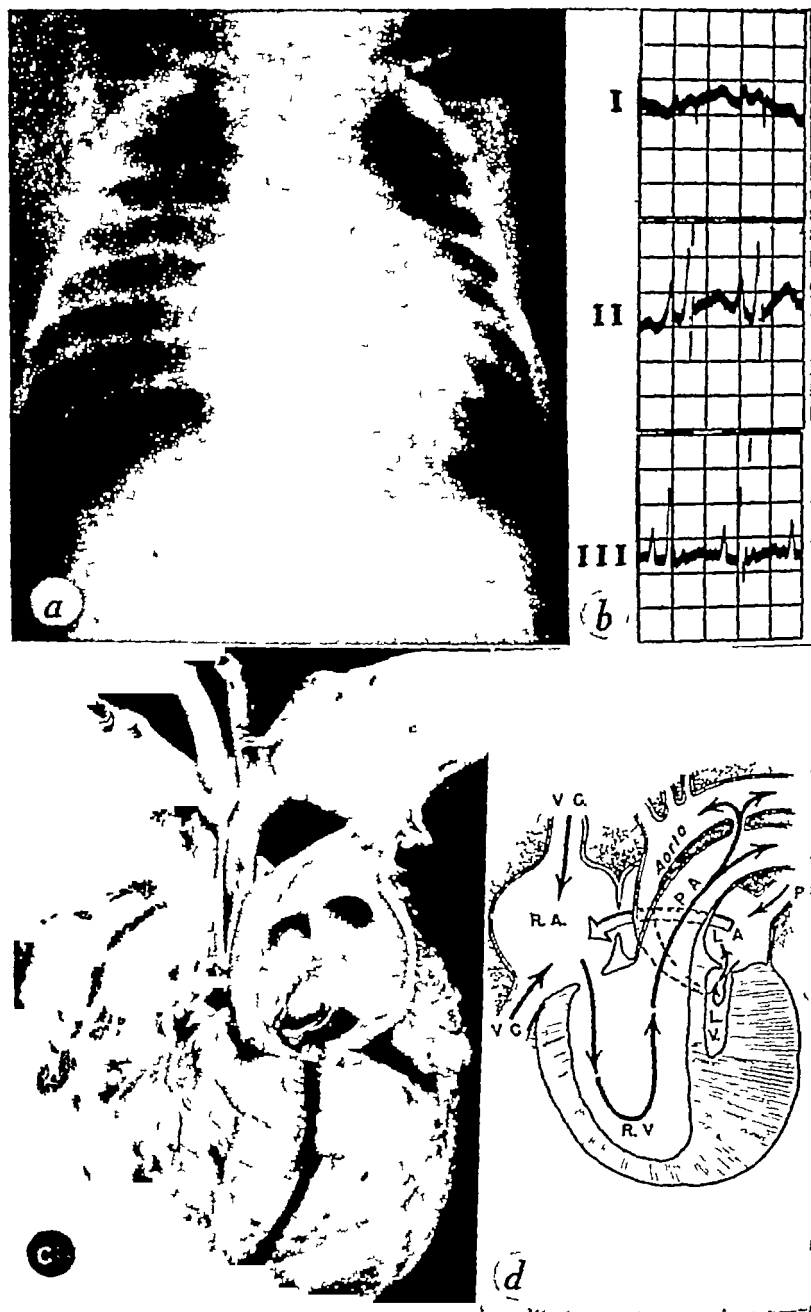


Fig 117 (Case 2) —*a*, Enlargement of the heart and prominence of the pulmonary conus *b*, Exaggerated P waves in leads II and III. There is right axis deviation *c*, The wide pulmonary artery and the hypoplastic aorta have been opened. The division of the pulmonary artery into right and left branches is demonstrated. The patent ductus arteriosus leads from the left pulmonary artery into the aorta which is dilated distal to the entrance of the ductus. Proximal to the ductus the aorta is narrow and the three major arteries from the arch of the aorta are illustrated *d*, Course of the blood through the heart.

the base of the heart. The edge of the liver was palpable 2 cm below the margin of the ribs. Urinalysis showed occasional erythrocytes and pus cells with a trace of albumin. The erythrocytes numbered 5,670,000 per cubic millimeter of blood and the hemoglobin measured 19 gm per 100 cc of blood. Roentgenograms of the chest revealed an enlarged heart with prominence of the pulmonary conus (fig 117a). The electrocardiogram revealed sinus tachycardia, exaggerated P waves in leads II and III. There was right axis deviation (fig 117b).

A diagnosis of congenital heart disease was made. In view of the presence of cardiac enlargement with a dominant right ventricle and indications of adequate pulmonary blood flow, a functioning single ventricle with aortic or mitral atresia or crossed transposition of the great vessels was considered as the most likely anatomic diagnosis. The infant failed to improve in the hospital and was dismissed to her home where she died one week later, on August 3, 1947, at the age of 4 months.

At postmortem examination the primary malformation in this heart was atresia of the aortic orifice by a diaphragm-like membrane which appeared to represent fusion of the aortic leaflets. The left ventricle was thick but the chamber was small. The mitral valve was diminutive. The left atrium communicated with the right atrium through a small foramen ovale. The right atrium, which received blood from the venae cavae as well as from the left atrium through the foramen ovale, was enlarged. The tricuspid orifice was normal and the right ventricle was enlarged. The pulmonary artery was wide and communicated with the aorta by means of a patent ductus arteriosus (fig 117c). The ascending aorta was hypoplastic. The orifices of the coronary arteries lay above the atretic aortic valve and received blood by reverse intra-aortic flow from the pulmonary artery by way of the patent ductus arteriosus.

Comment—The primary defect in this heart was atresia of the aortic orifice. Blood entering the left ventricle from the left atrium was trapped because this chamber had no outlet; consequently, there must have been a reflux of blood back through the mitral valve into the left atrium. As a result, all of the blood returning to the heart via the pulmonary veins was shunted through the foramen ovale into the right atrium where it mixed with the venous return from the systemic circulation. This mixed blood then entered the right ventricle and was pumped through the pulmonary artery, a portion traversing the ductus arteriosus into the aorta and the rest entering the pulmonary circuit (fig 117d).

This heart functioned as a single ventricle type, as did that reported in case 1. During fetal life, the entire volume of blood passed through the right ventricle, and this chamber provided the propulsion for the entire systemic circulation as well as for the pulmonary circuit. This resulted in enlargement of the right ventricle before birth. The course of the circulation remained essentially unchanged after birth and the enlarged heart was demonstrated by roentgenologic examination. While the pulmonary circulation was adequate, this infant exhibited constant cyanosis because of inadequate systemic blood flow and difficulty of the oxygenated blood in reaching the systemic circulation through the small foramen ovale. In the presence of this combination of cardiac defects the systemic blood pressure is usually low, as it must remain less than the pressure in the pulmonary circulation in order to assure flow of blood through the ductus arteriosus from the pulmonary artery into the aorta.

There are points of similarity between aortic atresia and mitral atresia as demonstrated in cases 1 and 2. These two abnormalities may exist together in the same heart, and the effect on the circulation is much the same as that mentioned for aortic atresia alone. The essential difference between case 1 and case 2 is that there was a ventricular septal defect with a closed ductus arteriosus in the infant with mitral atresia, and there was no ventricular septal defect but the ductus was patent in the case of aortic atresia. While there was right ventricular enlargement in each, the manner of mixture between venous and oxygenated blood was somewhat different in the two conditions.

CASE 3 —Atresia of the tricuspid orifice with rudimentary right ventricle, patent foramen ovale and ventricular septal defect (This case has been reported elsewhere ⁴)

A white female infant was born August 19, 1946, at full term. A loud, systolic murmur was present over the precordium. There were two brief spells of cyanosis during the first day of life, but thereafter the color of the skin remained normal during the neonatal period. There was no enlargement of the heart. The electrocardiogram made on August 22, 1946, showed left axis deviation (fig 118b). At the age of 6 weeks the infant's lips and nail beds were noticeably

blue, and there was some generalized cyanosis during crying spells. The mother described an occasional 'blue episode' lasting one to two hours during which the baby became dyspneic and coughed. The systolic murmur had become maximal in the third intercostal space just to the left of the sternum. A roentgenogram of the chest revealed absence of the pulmonary conus and a narrow vascular shadow above the heart (fig 118a). When the infant was 3 months old right hemiplegia suddenly developed and she was admitted to the hospital. At this time she was constantly cyanotic and dyspneic and did not improve with administration of oxygen. There were 5,170,000 erythrocytes per cubic millimeter and the hemoglobin measured 17.7 gm per 100 cc of blood. The electrocardiogram made on November 5, 1946, showed left axis deviation, notched QRS complexes in lead II and exaggerated P waves in leads II and III (fig 118b). She failed to improve and died on December 3, 1946, at the age of 3 months and 2 weeks.

At autopsy the primary malformation of the heart was atresia of the orifice of the tricuspid valve. No opening existed between the right atrium and the right ventricle (fig 118c). There was a patent foramen ovale (fig 118d). The left atrium communicated through the mitral orifice with the left ventricle which was enlarged and constituted the major portion of the ventricular part of the heart. The aorta communicated with the left ventricle. There was an ectopic ventricular septum in which a narrow slitlike defect existed in its membranous portion (fig 118e). Through the ventricular septal defect the left ventricle communicated with the diminutive right ventricle (fig 118f). The latter gave origin to the pulmonary artery. The ductus arteriosus was closed.

Comment—Functionally, this heart represents a single ventricle type. It is the counterpart of the anomaly occurring with mitral atresia, as the left ventricle rather than the right ventricle is dominant in tricuspid atresia. Figure 118g represents the course of the circulation in this heart as reconstructed from the anatomic findings. Since the tricuspid opening did not exist, the venous blood from the systemic circulation entered the right atrium by the venae cavae and passed through the foramen ovale into the left atrium. Oxygenated blood entered the left atrium from the pulmonary veins, mixed with the venous blood from the right atrium and then passed through the mitral orifice into the large left ventricle. The major portion of the contents of the left ventricle was pumped into the aorta but a small part was shunted

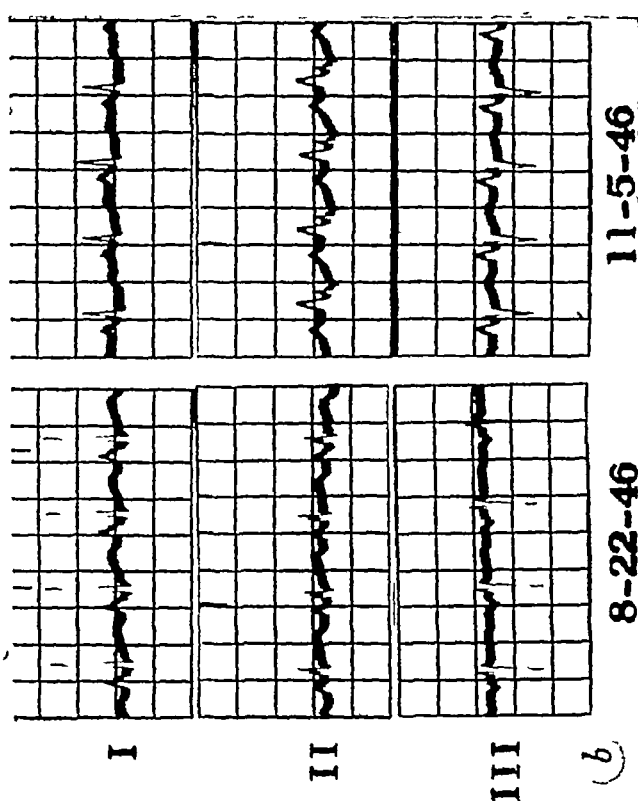


Fig 118 (Case 3) —a, Absence of the pulmonary conus and a narrow supracardiac shadow. The heart is not enlarged. b, The electrocardiogram on the left, made when the patient was 3 days old, reveals left axis deviation. In the one on the right, made when the patient was 3 months old, left axis deviation is still apparent. The P waves in leads II and III are exaggerated.

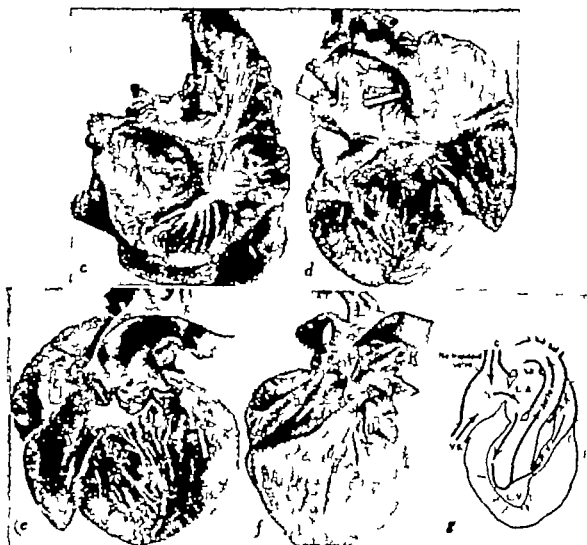


Fig. 118 (Continued from opposite page) —c, Interior of the right atrium of the heart. The probe is in the coronary sinus. At the expected location of the tricuspid orifice there is no opening and no tricuspid valvular tissue. The foramen ovale is patent. The right atrium is dilated. d, The left atrium and left ventricle are opened. There is a probe through the patent foramen ovale. The left atrium is dilated. Hypertrophy of the wall of the left ventricle and the large chamber are demonstrated. e, The inside of the left ventricle and aorta. The probe leads through the slitlike ventricular septal defect into the right ventricle beyond. f, The diminutive right ventricle and the pulmonary artery have been opened. A probe is in place in the ventricular septal defect and leads from the left ventricle beyond. g, Direction of the flow of blood through the heart. (Reprinted by permission from Edwards J. E., Dry T. J. and Logan G. B. Congenital atresia of the tricuspid orifice: report of a case. *Bull. Internat. Soc. M. Museums*. In press.)

through the small ventricular septal defect into the rudimentary right ventricle which served only as an outlet passage to the pulmonary artery. During fetal life the ductus arteriosus helped supply the pulmonary circulation. This condition probably prevailed for a time after birth, hence the pulmonary circulation was sufficient to prevent cyanosis until the ductus arteriosus began to close at approximately 6 weeks after birth. If the ductus had remained patent, this infant undoubtedly would have survived for a longer period.

The clinical features of tricuspid atresia are distinct and should lead to accurate diagnosis if properly evaluated. At birth the heart is not enlarged. The roentgenogram reveals no pulmonary conus and shows a narrow supracardiac vascular shadow in the anteroposterior position. In the left anterior oblique view, the supracardiac shadow remains narrow and the right ventricle appears small, as Taussig⁶ has pointed out. A cardiac murmur may or may not be present and is of no diagnostic importance. The electrocardiogram usually reveals left axis deviation, which occurs in no other type of congenital heart disease that produces cyanosis. The presence of cyanosis is another constant feature of tricuspid atresia.

This malformation of the heart is rare, 25 examples having been tabulated by Abbott in 1,000 cases of congenital heart disease. Since the pulmonary circulation is inadequate in infants with tricuspid atresia, an aortic-pulmonary artery anastomosis, such as the Blalock-Taussig or Potts procedure, would provide an increased flow of blood into the pulmonary circuit. Since this defect can be readily diagnosed during life, surgical anastomosis should be attempted in those cases in which there is marked cyanosis.

CASE 4 —Complete transposition of the aorta and pulmonary artery with patent ductus arteriosus and a defect in the membranous portion of the ventricular septum

A female infant born August 2, 1945, was the fifth child of healthy, 31 year old parents. The first 3 children were living and well but the fourth child had died at the age of 5 weeks because of congenital heart disease, although the exact anatomic lesion was unknown. The present infant was born at full term, the mother had had no known illnesses during the pregnancy. At birth the umbilical

cord was around the baby's neck and the baby was said to have been completely black, although her color rapidly improved after resuscitation. At the age of 5 weeks cyanotic spells developed and the physician discovered a heart murmur. She began to cough at the age of 6 weeks, difficult breathing developed and she became constantly cyanotic.

Examination at the clinic revealed an undernourished baby of 2 months whose weight was only 3,200 gm (7 pounds). She was moderately cyanotic. Her respirations were grunting. The skin was dry and loose. The heart was enlarged. A precordial systolic murmur loudest at the apex and audible in the left scapular region, was present. The lower edge of the liver was palpable 3 cm below the costal margin, but the spleen was not palpated. The erythrocytes numbered 4 000 000. A roentgenogram of the thorax showed marked enlargement of the heart with a narrow supracardiac shadow. The bronchovascular markings were increased (fig 119a). Electrocardiographic examination demonstrated sinus tachycardia with a rate of 178 per minute. There was right axis deviation (fig 119b). Shortly after admission to the hospital the temperature rose to 103.6° F and the infant became moribund, dying October 3, 1945 thirty-six hours after admission, at the age of 2 months.

At autopsy the pathologic features of this heart were characteristic of complete transposition of the great vessels. The aorta arose exclusively from the right ventricle (fig 119c). The pulmonary artery arose from the left ventricle. The ascending aorta was abnormally related to the pulmonary artery in that the former lay directly in front of the latter. There was a defect in the membranous portion of the ventricular septum as shown in figure 119d. There was a mild degree of patency of the ductus arteriosus.

Comment—In this abnormality of the heart the blood entered the right atrium from the venae cavae, then entered the right ventricle through the tricuspid orifice (fig 119e). From the right ventricle the blood was pumped into the aorta and into the systemic circulation, returning again to the right atrium without oxygenation in the lungs. Blood entering the left atrium from the pulmonary veins entered the left ventricle and was recirculated through the pulmonary system. There was no crossing of the systemic blood to the pulmonary circuit except through the ventricular septal defect and through the ductus arteriosus. Without an additional anomaly, complete transposition of the great vessels is not compatible with life after birth, because the systems do not

cross and oxygenated blood cannot reach the body. In this case the patent ductus arteriosus allowed some mixture of the blood from the two systems, and this mixture was en-

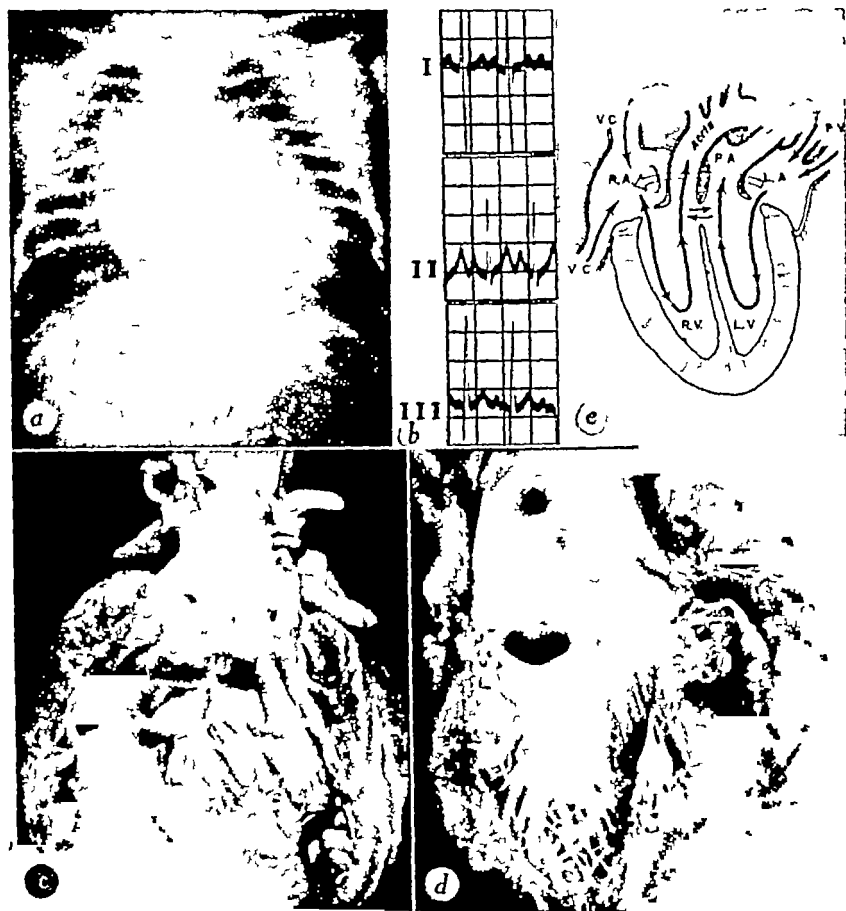


Fig. 119 (Case 4)—*a*, Enlargement of the heart, a narrow supracardiac shadow and increased bronchovascular markings are evident. *b*, Electrocardiogram, made at the age of 2 months, shows right axis deviation. *c*, The right ventricle has been opened and the aorta can be seen originating from this chamber. There is a defect in the membranous part of the ventricular septum. The orifices of the coronary arteries are visible, arising from the aorta. *d*, The inside of the left ventricle and the pulmonary artery is shown. The defect of the ventricular septum is visible just under the orifice of the pulmonary artery. *e*, Direction of blood flow through the heart.

hanced by the ventricular septal defect. During fetal life the circulation is not handicapped by cross transposition of the great vessels. Oxygenated blood from the placenta enters the right atrium and ventricle and is pumped into the aorta to supply the systemic circulation, a portion crossing into the

pulmonary circuit via the ductus arteriosus, the left ventricle receives blood from the pulmonary circuit and provides the force necessary to force the blood through the pulmonary artery into the pulmonary circulation. This situation is similar to the normal conditions except that the two ventricles are functionally reversed. No heart strain occurs before birth, consequently, there is no cardiac enlargement in the newborn baby.

Complete transposition of the aorta and pulmonary artery produces cyanosis at birth unless there is a septal defect. With a septal defect some mixture of blood results and color may remain good in infancy, but, since the systemic blood is recirculated without passing through the pulmonary system, cyanosis tends to become more evident as time passes. The cyanosis is accentuated with stress, such as that from crying or nursing. Taussig⁷ has pointed out that the color of the lower extremities may be better than that of the upper part of the body because a shunt of oxygenated blood through the ductus arteriosus usually enters the descending aorta and is less likely to be distributed to the vessels arising from the arch of the aorta.

Diagnostic features of transposition of the aorta and pulmonary artery consist of cyanosis, which may become more intense in the upper part of the body, at an early age, rapid enlargement of the heart, particularly the right atrium and right ventricle, and roentgenographic evidence of an enlarged heart, with a narrow supracardiac shadow and absent conus in the anteroposterior view, and enlargement of the right ventricle with widening of the vascular shadow in the left anterior oblique projection. Murmurs are variable and depend on the associated anomalies. The electrocardiogram is not characteristic.

Most infants with complete transposition of the great vessels survive only a few months after birth. Closure of the ductus arteriosus reduces the amount of crossing of the two circulations so that continued survival is dependent upon the presence of additional anomalies which allow mixture of systemic blood with the pulmonary blood. Survival for a number of years is possible with a large atrial septal defect. This fact suggests that a possible surgical approach to this

condition might be the creation of an atrial septal defect to allow mixture of the oxygenated blood of the pulmonary circulation with the venous blood of the systemic circuit. On the other hand, many infants with transposition of the great vessels and a patent foramen ovale have failed to survive the neonatal period, so there is no assurance that this additional anomaly will prolong life.

SUMMARY

Reports of 4 cases have been presented which demonstrate four different types of uncommon congenital malformations of the heart. Clinical and pathologic features have been correlated in an effort to clarify the altered physiology and to emphasize the diagnostic features of mitral atresia, aortic atresia, tricuspid atresia and transposition of the great vessels. The presence of cyanosis and the configuration of the heart on roentgenographic and roentgenoscopic examination provide the most accurate means of evaluation. Cardiac murmurs are of no importance in differentiating these anomalies in infancy and the electrocardiogram is of little aid except in the case of tricuspid atresia, in which the left axis deviation is diagnostic.

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ATRIAL SEPTAL DEFECTS

THOMAS J DRY

THE division of the primitive atrium occurs in a manner that not only allows blood to flow from the right to the left atrium during antenatal life but also prevents the flow of blood from the left to the right atrium after birth. Thus the same flaplike structure, the septum primum, which is readily pushed aside by the directional force of the fetal circulation and which prevents regurgitation of blood back into the right atrium, is forced against the foramen ovale (which is an aperture in the foramen secundum) as soon as the pressure in the right atrium falls below that in the left atrium. This event occurs when the pulmonary circulation begins to function in the newborn at a time when peripheral resistance in the pulmonary circuit falls and when peripheral resistance in the systemic circulation rises. During the first year of life the foramen ovale normally is large enough to admit a probe and in about 20 per cent of persons such a condition persists indefinitely but is of no clinical importance except when under exceptional circumstances the slit may be temporarily opened by a rise of right atrial pressure over that in the left atrium, as for example when an embolus becomes lodged in the pulmonary artery. It is under such conditions that an embolus may also escape through the foramen ovale and enter the systemic circulation (paradoxical embolism) (Fig. 120).

as well as the history in cases of atrial septal defect are somewhat variable and the following cases were selected to illustrate the secondary manifestations and their outcome



Fig 120 —Interior of right atrium An elongated thrombus is projecting through the foramen ovale

REPORT OF CASES

CASE 1 —Atrial septal defect with easily recognizable physical signs but with relatively mild symptoms

At the age of 16 years, the patient in this case was first told, while he was being examined for life insurance, that something was wrong with his heart. There was no history of rheumatic fever prior or subsequent to this time. At the age of 30 years he was told again, in the course of a routine physical examination, that his heart was enlarged. At that time, dyspnea was occurring as a result of rather strenuous effort but his only complaint was that he was aware of

'missed beats" at night. At the age of 39 years he had meningitis. During the five years before he came to the Clinic there had not been any progression in his dyspnea. He came to the Clinic at the age of 44 years because of repeated attacks of biliary colic. A cholecystectomy including exploration of the common bile duct was performed without incident.

When the patient was examined at the Clinic it was noted that he was well developed and weighed 200 pounds (90.7 kg). His blood pressure was 112 mm of mercury systolic and 78 mm diastolic. Examination of the heart revealed a systolic murmur at the base and at the pulmonary area, accentuation of the second pulmonic sound, a palpable pulsation in the second and third left interspaces, general cardiac enlargement with absent aortic knob and marked increase in the pulmonary conus shadow (fig. 121a). The hilar vessels were enlarged and roentgenoscopic examination disclosed marked pulsations in these vessels. The leukocyte count was 7,000 per cubic millimeter of blood and the value for the hemoglobin was 16 gm per 100 cc. of blood. An electrocardiogram (fig. 121b) revealed a cardiac rate of 54 per minute, impaired ventricular conduction, a QRS complex of 0.12 second, low amplitude of T waves in leads I and II, diphasic T waves in lead III, and positive T waves in leads CR₂ and CR₃. The clinical diagnosis was an atrial septal defect.

After the gallbladder had been removed, the right atrium was catheterized through the median cephalic vein (fig. 121c). The oxygen saturation of the blood in the right atrium was 84 per cent while that of the blood in the superior vena cava was only 63 per cent. This finding confirmed the diagnosis of an atrial septal defect.

This case is an example of an atrial septal defect which produced minor cardiac symptoms with rather little tendency to progression but with definite signs indicative of an abnormal cardiovascular physiologic status. The capacity for exercise, considering the size of the heart, is in contrast with that in cases of acquired heart disease in which enlargement of the heart is as great as it was in this case.

In a case in which the patient is acyanotic and does not have congestive heart failure, the recognition of atrial septal defect depends on the following clinical features, which were well represented in this case: (1) a systolic basal murmur, (2) an accentuated second sound in the pulmonic area which occasionally is associated with a soft diastolic murmur of pulmonary insufficiency, (3) marked enlargement of the atria.

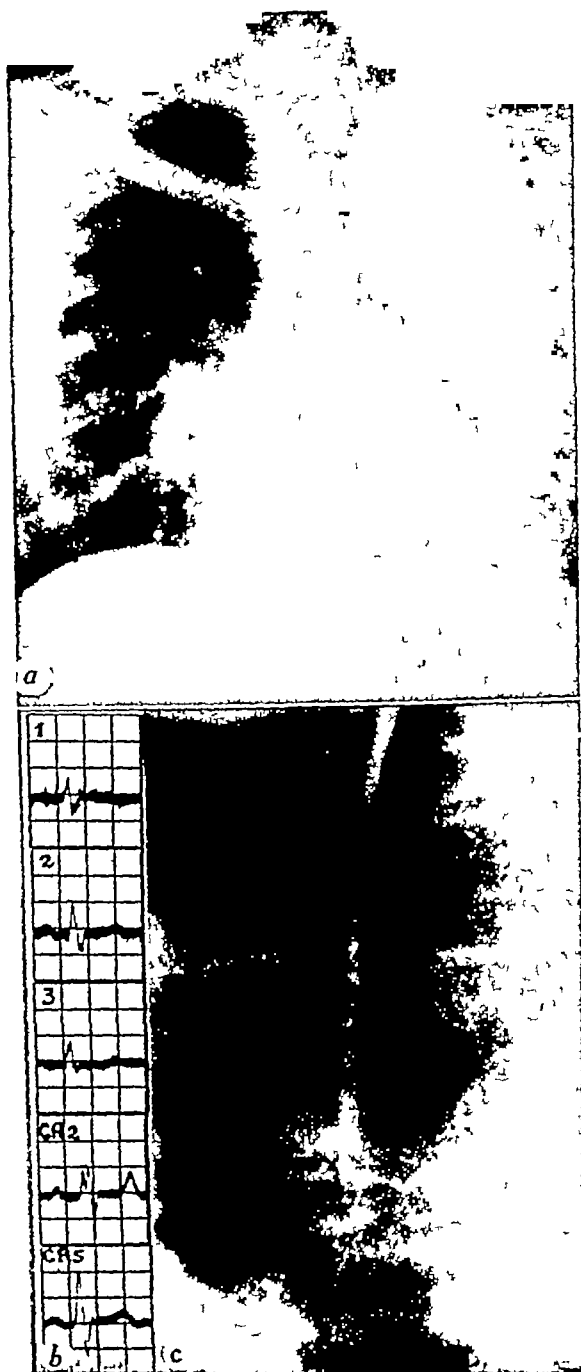


Fig 121 —Roentgenogram showing cardiac enlargement, fullness of the pulmonary conus, prominent hilar vessels and absence of prominence of aortic knob in case 1 *b*, Electrocardiogram showing bundle branch block, T waves of low amplitude in leads I and II, and diphasic T wave in lead III (case 1) *c*, Catheter inserted into right atrium in case 1

(especially the right atrium), the right ventricle and the pulmonary artery, (4) accentuation of pulsations in the hilar vessels, and (5) an electrocardiographic pattern of right ventricular strain, which often is associated with right bundle-branch block. Catheterization of the chambers of the heart is important in distinguishing an atrial septal defect from patency of the ductus arteriosus in cases in which the characteristic machinery murmur diagnostic of the latter anomaly is, for reasons not yet known, replaced by a systolic basal murmur or when the electrocardiogram reveals right axis deviation. The same method will distinguish an atrial septal defect from lesions such as primary cor pulmonale and so-called idiopathic dilatation of the pulmonary artery. In secondary cor pulmonale, the underlying pulmonary lesion which causes the pulmonary hypertension usually is obvious from the history and the physical signs. The commonest type of arrhythmia observed in cases of atrial septal defect is auricular fibrillation. In fact, atrial septal defect is the congenital anomaly which most frequently causes fibrillation of the auricles. The probability that this arrhythmia will develop increases if mitral endocarditis coexists (Lutembacher's syndrome).

Other electrocardiographic findings which may be present are those seen in cases in which chronic right ventricular strain is due to other causes. These findings are (1) right axis deviation, (2) large, often bifid, P waves, (3) prolongation of the P-R interval, which was noted in 19 of 53 cases reported by Bedford, Papp and Parkinson, (4) right bundle-branch block and (5) inversion of the T waves in leads II and III. The ventricular conduction defect is considered by most authors to be a sequel of atrial septal defect rather than a part of the lesion. Case 2 shows that this however, is not always true since the conduction defect was clearly evident when the patient was 9 years old (fig. 122a).

CASE 2 — Atrial septal defect, incapacitation due to limited cardiac reserve and to many functional symptoms, sudden and unexpected death.

The patient in this case was seen at the Clinic on numerous occasions over a period of twenty-seven years. The patient first was

observed at the Clinic in 1920, when she was 9 years of age. At that time, she was brought to the Clinic because she had chronic eczematoid dermatitis. Examination at that time disclosed diffuse cardiac pulsation and a "rough, mitral, systolic murmur." Physical and roentgenologic examination revealed that the heart was enlarged. A diagnosis of mitral regurgitation was made. There was no history of rheumatic fever.

The same findings were observed when the patient was examined at the Clinic a year later. One consultant recorded the presence of a rough basal systolic murmur in addition to the apical murmur and also reported that the second pulmonic sound was louder than the second aortic sound. A tonsillectomy was performed at that time.

During the years that followed, her visits to the Clinic were occasioned by a variety of reasons. She was hospitalized many times because of exacerbations of eczematoid dermatitis, in 1932, an exploratory laparotomy disclosed an inflammatory mass in the right side of the pelvis. Although she frequently returned as an out-patient because of various intercurrent illnesses that were quite independent of her cardiac condition, she never failed to complain of symptoms referable to her heart. Since childhood, her tolerance to exertion had been limited by dyspnea and especially by consciousness of tachycardia. As she grew into adulthood, the tachycardia became a prominent symptom and was associated with stabbing pains in the left mammary region. She had attacks of "shortness of breath" associated with hyperventilation tetany. There was frequent reference to gastro-intestinal symptoms for which there was no organic basis and to fatigability. While cardiac reserve was obviously limited, examination never disclosed any evidence of congestive heart failure and cyanosis was not noted at any time.

In 1946, the cardiac findings were essentially the same as those which had been noted during childhood. Marked precordial pulsation was visible. This was especially obvious because the patient was of the asthenic type. Auscultation revealed a coarse systolic basal murmur and marked accentuation of the second pulmonic sound. The first mitral sound was split but the auscultatory findings at the apex were not prominent enough to substantiate the presence of organic mitral endocarditis.

At this time, the value for the hemoglobin was 15 gm per 100 cc of blood and the erythrocytes numbered 4,140,000 per cubic millimeter of blood. Roentgenologic examination revealed cardiac enlargement with marked prominence of the upper left border and of the pulmonary vascular markings (fig 122b). The blood pressure on numerous examinations was always found to be within normal limits. Electrocardiograms that were made on three occasions are illustrated in figure 122a. They basically show essentially the same

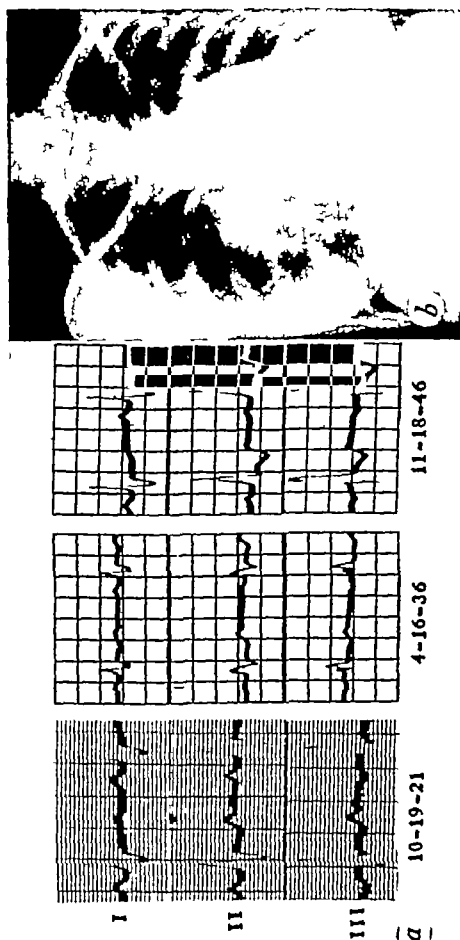


Fig 122.—a Electrocardiograms made on three occasions in case 2. The one made in 1921 shows right bundle-branch block a diphaseic T wave in lead II and an inverted T wave in lead III. The electrocardiogram made in 1936 shows right bundle-branch block and diphaseic T waves in leads I, II, and III. The one made in 1946 shows right bundle-branch block a diphaseic T wave in lead I and deeply inverted T waves in leads II and III. b Roentgenogram made in 1946 (case 2) showing cardiac enlargement marked bulging of the pulmonary conus prominence of hilar vessels and absence of aortic knob.

pattern and reveal right bundle-branch block with a QRS spread of 0.12 second. The secondary effects of right ventricular strain are more evident in the electrocardiogram that was made in 1936 than they are in the one that was made in 1921, and they are likewise more evident in the roentgenogram that was made in 1946 than they are in the one that was made in 1936. These electrocardiograms reveal a progressive trend toward inversion of the T waves. This first was indicated by inversion of the T wave in lead III, it later was manifested by inversion of the T wave in lead II, and finally by a diphasic T wave in lead I.

In the later years in which this patient was observed at the Clinic, it was the consensus of the consultants that she had congenital heart disease which produced a rather typical clinical picture of an atrial septal defect. The patient was last seen at the Clinic in July, 1947, when she was 36 years old. At that time, it was felt that her cardiac status was essentially the same as it had been at the time of her previous examination at the Clinic.

The patient was found dead at her home on September 12, 1947. Necropsy revealed that the heart weighed 550 gm (normal weight is 234 gm). The right ventricle was markedly hypertrophied and moderately dilated. Both atria were moderately dilated. The foramen ovale measured 4 cm in diameter. The mitral valve was normal except that a slight degree of thickening was present at the free edge of the valve. There was no adherence of the leaflets, and the chordae tendineae were normal.

Several writers^{1,5,6} have stressed the constitutional delicacy of patients who have an atrial septal defect. The patient in case 2 as well as the patients in cases 3 and 4 conformed to this description, but this cannot be considered of diagnostic aid since there are too many exceptions to the rule. Although Bedford and his co-workers said that too much emphasis had been placed on such an association, the clinical picture is quite striking in cases in which patients have a frail habitus. Not infrequently, such patients have many functional symptoms which add to the incapacitation already imposed by the cardiac defect.

Case 2 illustrates the rather frequent occurrence of sudden and unexpected death in cases of atrial septal defect in which little in the way of progression of symptoms has been evident to aid in the anticipation of such an event. Paradoxically, these patients may withstand major surgical procedures without incident, as did the patient in this case.

CASE 3—*Atrial septal defect, complicated by paroxysmal tachycardia, sudden death*

A woman, aged 24 years, first came to the Clinic in 1938. She had been treated for rheumatic fever at the age of 15 years. The exact details of this illness were however not stated. Since the age of 17 years she had been aware of palpitation. This had been a constant annoyance and as time passed she had become more and more inactive because of easy fatigability and because of the occurrence of dyspnea on exertion. Because of these symptoms she had dis-

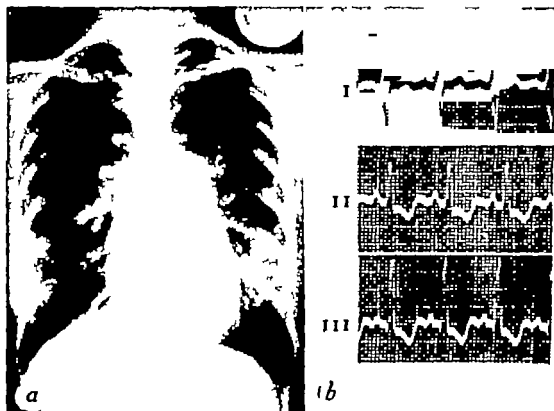


Fig 123—*a* Roentgenogram in case 3 showing a moderate degree of cardiac enlargement marked bulging of the pulmonary conus prominence of the hilar vessels and absence of aortic knob. *b* Electrocardiogram showing right axis deviation and inversion of T waves in leads II and III (case 3)

continued work as telephone operator two years before she came to the Clinic. There was no history of dependent edema, cyanosis or hemoptysis. A year before she came to the Clinic, she had had an attack of very rapid heart action which had begun and ended abruptly and had lasted about one hour. While she was being examined at the Clinic a second paroxysm of tachycardia developed and the ventricular rate increased to 160 beats per minute. She was hospitalized for further observation and treatment. Before an electrocardiogram could be made the rhythm had reverted to normal and the exact type of ectopic rhythm that had been present during the paroxysm could not be identified.

Examination disclosed that the heart was enlarged to the left

A loud blowing systolic murmur was heard at the apex. A review of the roentgenogram of the thorax revealed cardiac enlargement, marked bulging in the conus region, and prominent hilar vascular markings (fig 123a). The electrocardiogram (fig 123b) disclosed a cardiac rate of 100, right axis deviation, inverted T waves in leads II and III, slurred QRS complexes in leads I and III and notched complexes in lead III.

The diagnosis was chronic rheumatic endocarditis with mitral stenosis and insufficiency. The view was further expressed that cardiac reserve was markedly limited although no signs of decompensation were present. It was considered desirable to prevent recurrences of ectopic rhythm which might very readily precipitate congestive heart failure. Quinidine sulfate was administered orally for this purpose. On the day the administration of this drug was started, the patient received three doses of 3 grains (0.2 gm) each, on the following day, she received four doses of 4 grains (0.26 gm) each. The pulse rate dropped to 80 beats per minute and the patient seemed quite comfortable. At 3 a.m. on the following day, that is, five hours after the last dose of quinidine was administered, gasping sounds attracted the attention of the nurse on duty. The nurse rushed to the patient's room but the patient died in a few seconds.

Necropsy revealed that the heart weighed 322 gm. The right ventricle was hypertrophied and dilated. The mitral valve was thickened and fibrosed along the free edge. As a result, the preliminary impression at necropsy was that there was an associated mitral endocarditis and that the findings fulfilled the criteria for a diagnosis of Lutembacher's disease. Further studies revealed, however, that there was no significant shortening or fusion of the chordae tendineae. The mitral valve was 8.3 cm in diameter. The tricuspid valve was dilated. The patient had a patent foramen ovale which was 3.3 cm in diameter.

Case 3 is an example of atrial septal defect that caused a disturbance of cardiac rhythm which probably was the immediate cause of death. The exact type of arrhythmia was not determined but since the ventricular rate was 160 per minute one can be reasonably certain that it was an ectopic rhythm. The patient was only 24 years old and the thickening of the free edge of the leaflets of the mitral valve was suggestive of rheumatic endocarditis but microscopic examination failed to corroborate this impression. It is probable that the incidence of Lutembacher's disease has been believed to be higher than it actually is, because of similar findings in cases of atrial septal defect.

CASE 4 — *Atrial septal defect complicated by cerebral abscess*

This case has been reported previously by Ingham and by Gates Rogers and Edwards. The patient in this case was a woman who first was brought to the Clinic in 1916, at the age of 19 years because of nervousness, tachycardia, 'marked dyspnea and palpitation on exertion', constant headache and loss of strength. She had been confined to bed for three weeks previously and she was in a wheel chair when she first was observed at the Clinic. When she was a young child, her parents had been told that her heart was twice its normal size.

Her lips and fingers were cyanotic. This condition was said to have been present since birth. Roentgenographic examination disclosed enlargement of the heart and fullness in the region of the pulmonary conus. The cardiac rate was rapid. The second pulmonic sound was markedly accentuated but no murmur could be detected. A diagnosis of hyperthyroidism was considered but the presence of this condition was ruled out. The term "neurotic temperament" was used in the clinical record. The erythrocyte count was more than 5,000,000 on two occasions.

These findings were interpreted as indicative of congenital heart disease but no opinion was expressed as to the type. It was apparent from the record that the disability was considered to be somewhat out of proportion to the physical findings and she was encouraged to resume activity.

She was not seen again at the Clinic until about eighteen years later. As far as her cardiac symptoms were considered she had got along extraordinarily well in the meantime. She had been able to do housework and experienced only mild palpitation on exertion. At this time, she was described as being poorly developed and under-nourished. There was slight cyanosis of the lips and fingers. The heart was described as moderately enlarged and having the configuration of a heart with disease of the mitral valve. Auscultation disclosed a soft basal systolic murmur and marked accentuation of the second pulmonic sound. There was no clubbing of the fingers or toes. The value for the hemoglobin was 17.5 gm per 100 cc of blood and the erythrocyte count was 5,030,000. The electrocardiogram (fig. 124) showed a rate of 72, marked sinus arrhythmia, right axis deviation, inverted P waves in leads II and III, T waves of low amplitude in lead I and diphasic T waves in leads II and III.

Two years later, that is, in 1936, when the patient was 39 years old, she was readmitted after an influenza-like illness of a week's duration. Right hemiparesis, aphasia and right homonymous hemianopsia had developed gradually in the course of the illness. Encephalography did not reveal any air over the left hemisphere. A left subtemporal decompression revealed a

white exudate along the cortical vessels. The nature of the underlying pathologic change was not determined. After temporary improvement, her physical condition became steadily worse and she died two weeks after the operation was performed.

Necropsy disclosed a solitary abscess in the left temporoparietal region. Her heart weighed 310 gm (normal weight is 250 gm). Necropsy also disclosed a moderate degree of hypertrophy of the right ventricle. The pulmonary arteries were dilated owing to the presence of advanced arteriosclerosis. The foramen ovale was patent and measured 2 by 3 cm. There was no evidence of subacute bacterial endocarditis.

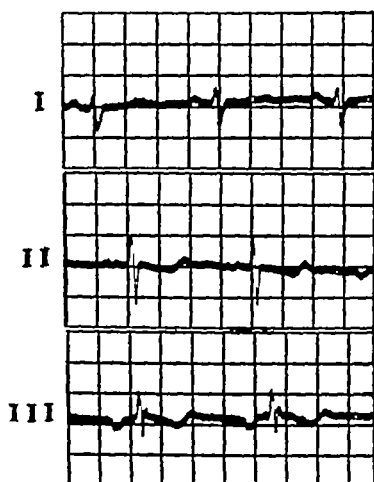


Fig 124 —Right axis deviation, T wave of low amplitude and diphasic T waves in leads II and III in case 4

The occurrence of a solitary abscess of the brain in association with congenital heart disease was reported as early as 1814. An analysis of the cases reported in the literature reveals that abscess of the brain can occur whenever there is a congenital anomaly which allows recirculation of the venous blood in the systemic circulation.³ It is assumed that the pulmonary circulation normally filters out organisms which may be circulating in the blood stream.

The development of the abscess of the brain in case 4 is in keeping with certain other clinical features noted as early as the patient's first examination at the Clinic, namely, the presence of mild cyanosis and polycythemia, which indicated some degree of venous arterial shunt, which is usually not a feature of atrial septal defect until decompensation of the right ventricle occurs. It is quite remarkable that, despite these features, congestive heart failure never developed dur-

ing the twenty years that she lived after the original observations were made at the Clinic

The anatomic and physiologic arrangement present in this case might very well explain how paradoxical embolism may occur in cases in which there is a venous arterial shunt.

CASE 5 — Atrial septal defect complicated by rheumatic mitral stenosis (Lutembacher's syndrome) auricular fibrillation and congestive heart failure, sudden death

A man 50 years of age, came to the Clinic in 1941 and was admitted to a hospital because of 'a dropsical condition and rapid heart beat'. There was no definite history of rheumatic fever. Between 1925 and 1931, he had had four attacks of rapid, irregular heart action, each of which had lasted only from fifteen to twenty minutes. Subsequent attacks had occurred more frequently and had lasted for from several hours to fifteen hours. During these paroxysms of tachycardia, he had become very dyspneic, a symptom which, however, had disappeared after restoration of normal cardiac action. He had taken digitalis at various times but he had not taken this drug after 1936. Since 1931, the patient had been taking quinidine in varying doses. During the four months before the patient came to the Clinic he had been taking from 20 to 30 grains (1.3 to 2 gm.) of this drug daily because the paroxysms of tachycardia had increased in frequency and duration. Edema of the ankles first had occurred in the spring of 1941 but it had not increased appreciably until two weeks before the patient came to the Clinic.

Physical examination revealed advanced cardiac decompensation, ascites, peripheral edema, engorgement of the liver and rales at the bases of both lungs. The heart extended 2 cm. to the left of the nipple line, and the auricles were fibrillating rapidly. The first mitral sound was described as 'sharp'.

The blood pressure was approximately 100 mm. systolic and 80 mm. diastolic. The erythrocyte count was 3,920,000 and the leukocyte count was 4,000. The value for the hemoglobin was 11.7 gm. per 100 cc. of blood. A routine flocculation test did not disclose any evidence of syphilis. Roentgenographic examination of the thorax revealed that the heart extended 11 cm. to the right of the midsternal line and 12 cm. to the left (fig. 125a). There was evidence of marked congestion in both sides of the thorax. An electrocardiogram disclosed a cardiac rate of 131, auricular fibrillation, impaired ventricular conduction, QRS complexes of 0.16 second, iso-electric T waves in lead I, inverted T waves in leads II and III, QRS complexes of low amplitude in leads I, II and III, inverted T waves and an absence of S waves in lead CR₁, and indefinite T waves and QRS complexes of low amplitude in lead CR₂ (fig. 125b).

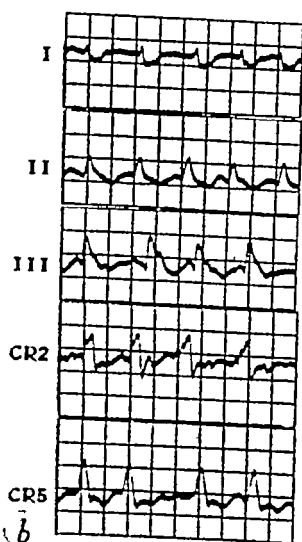


Fig 125 —a, Roentgenogram showing, huge heart, pulmonary congestion, fullness of the pulmonary conus and absence of aortic knob in case 5 b, Electrocardiogram showing auricular fibrillation, impaired ventricular conduction (QRS complex of 0.16 second), iso-electric T wave in lead I, inverted T waves in leads II and III, indefinite T wave in lead CR₂ and inverted T wave in lead CR₅ (case 5) c, Interior of left atrium and left ventricle showing a patent foramen ovale (case 5) The mitral valve has been opened. One may observe thickening and fusion of the mitral valve and shortening, fusion and thickening of the mitral chordae.

The consultant made a diagnosis of chronic rheumatic endocarditis with mitral stenosis and insufficiency. Under the usual therapeutic program, which included digitalization and the administration of diuretics the patient appeared to be responding satisfactorily but he died suddenly on the ninth day after his admission to the hospital.

Necropsy disclosed that the heart weighed 740 gm (normal weight is 270 gm). The right ventricle and right auricle were extremely dilated but the left ventricle and left auricle were only slightly dilated. The rings of the pulmonic and tricuspid valves were widely dilated, as was the pulmonary artery itself. There was an interauricular communication representing a patent foramen ovale which was 5.5 cm in diameter. Examination of the mitral valve revealed chronic rheumatic endocarditis, moderate thickening and fusion of the valve leaflets and thickening, shortening and adhesion of the chordae tendineae, a picture that is typical of mitral stenosis (fig. 125c).

Case 5 is a true example of Lutembacher's syndrome because the auricular septal defect was large and the existence of mitral stenosis was confirmed pathologically. The clinical course was undoubtedly influenced by the presence of rheumatic heart disease. Auricular fibrillation at first occurred paroxysmally but it eventually became permanent. The mode of death, however, was more characteristic of atrial septal defect than of mitral stenosis since it is quite unusual for a patient who has rheumatic mitral disease to die during the first episode of congestive heart failure in which adequate treatment is being employed.

GENERAL COMMENT

Among congenital cardiac anomalies the incidence of atrial septal defects is rather high even if one excludes cases in which the opening in the interatrial septum is merely large enough to permit the insertion of a probe and cases in which the opening is too small to produce secondary effects. A review of 133 cases of all types of congenital anomalies of the heart and great vessels in which the patients were observed at the Clinic has revealed 25 cases in which there was an atrial septal defect that was large enough to produce symptoms. In 18 of the 25 cases the patients were females. Bedford, Papp and Parkinson reported a series of 53 similar cases and said that 40 of the 53 patients were females.

The diagnostic criteria and clinical variations of atrial

septal defect have been outlined and need no further comment. Criteria for determining the prognostic trends are not particularly reliable or easy to define, which is a feature common to many other types of cardiac anomalies. The development of certain complications is quite unpredictable and sudden death is not uncommon. Nevertheless, many such patients who have atrial septal defects reach adult life and some die of unrelated diseases at an advanced age. The life span of the patients in our series of 25 cases was as follows: five died between the ages of one day and seven years, two lived into the third decade, four, into the fourth decade, two, into the fifth decade, five, into the sixth decade, four, into the seventh decade of life, while three reached the age of 70 years or more.

It is of interest to note that there was evidence of impaired intraventricular conduction in 3 of the 5 cases that have been reported in this paper. Bedford, Papp and Parkinson found an abnormally wide QRS complex in approximately half of the 53 cases which they reported. This electrocardiographic abnormality, therefore, must be considered to be of some importance in the differential diagnosis of congenital abnormalities of the heart.

At the present time, conservative and conventional types of therapy should be employed in cases of atrial septal defects. That a defect of the atrial septum will one day lend itself to surgical closure may yet prove to be more than an optimistic prediction, despite the technical difficulties which make such a procedure impossible today.

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VARIATIONS IN THE CLINICAL AND PATHOLOGIC PICTURE OF PATENT DUCTUS ARTERIOSUS

HOWARD B BURCHELL

THE successful surgical treatment of patent ductus arteriosus over the past decade has focused attention upon the common clinical picture of this congenital lesion. The stereotyped syndrome of a continuous arteriovenous type of murmur and thrill, a wide pulse pressure and collapsing pulse, with roentgenographic and electrocardiographic evidence that is consistent with slight to moderate left ventricular enlargement, is well recognized. In a child the chances that such a combination of findings would be caused by some lesion other than a patent ductus arteriosus, such as a defect in the truncus septum or an intrathoracic congenital arteriovenous fistula, would be very slight.

However, in addition to the common, or typical, picture of a patent ductus arteriosus, there are certain atypical cases in which the secondary effects of the patent ductus often clinically outshadow the primary physiologic fault. This fact together with the interest any clinician will have in the function of a patent ductus when it is associated with other congenital defects, creates a large field for diagnostic endeavors and clinical investigations. Indeed, to carry out a study on patent ductus arteriosus from the stage of embryologic development through the period of primary circulatory aberrations and their related anatomic adjustments to the stage of late pathologic changes would prepare one most thoroughly for most of the problems in cardiology.

Perhaps the rather constant position of the ductus arteriosus on the left side as a representation of the embryonic left pulmonary arch even when there is a right aortic arch, could be related to embryonic ventricular directional ejection. The ductus arteriosus may be responsible for a right aorta commonly crossing behind the trachea and esophagus to pass down the thorax on the left side. Thus, one might suspect that a right aortic arch that did descend on the right side of the thorax and was associated with a right ductus arteriosus would be commonly associated with a severe intracardiac

defect, particularly a defect in the partition of the truncus septum, resulting in pulmonary stenosis. A bilateral ductus arteriosus has been reported in association with a severe intracardiac anomaly and is mentioned as a medical curiosity¹⁶. In the realm of acyanotic heart disease, however, one might expect to find sometimes a patent left-sided ductus associated with a right aortic arch, with a left subclavian artery arising from the dorsal aorta but without any associated intracardiac defect, and it might be possible to recognize such a lesion clinically. Such an anomaly has been reported (fig 126). The

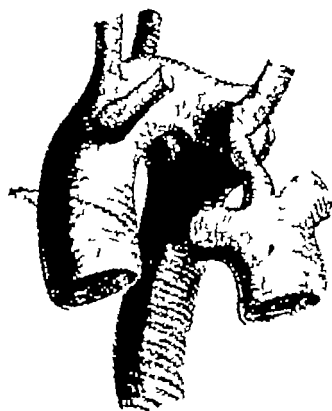


Fig 126 —A reproduction illustrating a left ductus arteriosus in association with a right aortic arch and an anomalous left subclavian artery. The latter, in its proximal portion represents persistence of the dorsal portion of the left fourth arch (From Quain, Richard. *The anatomy of the arteries of the human body and its applications to pathology and operative surgery*, with a series of lithographic drawings. London, Taylor & Walton, 1844, 550 pp.)

mirror picture of such a lesion, that is, a right-sided ligamentum arteriosum and right descending thoracic aorta associated with a left aortic arch, has been observed in 1 case in which the lesion was studied in detail by Edwards⁸.

A persistent patency of the ductus arteriosus in cases of coarctation of the aorta in childhood is not rare, the ductus being either proximal or distal to the aortic stricture. When the ductus is proximal, the physiologic effect is similar but accentuated, as in uncomplicated ductus, but when the ductus is distal to the coarctation the circulatory dynamics are profoundly altered.

While in older patients with coarctation a basal diastolic murmur is usually indicative of an insufficient bicuspid aortic valve, in children such a murmur should make one suspect the presence of a small patent ductus proximal to the stricture. When the diagnosis of ductus arteriosus is made in children the routine examination for the abdominal and femoral pulses should never be neglected.

Atresia or marked stricture of the aorta proximal to a widely patent ductus, the so-called infantile type of coarctation, produces an interesting physiologic condition, the circulation having a basic resemblance to that of an alligator, in which 1 of the 2 aortae arises from the right ventricle to distribute venous blood to the left upper extremity and lower part of the body. In a recently observed girl, 7 years of age, of normal development and good exercise tolerance a coarctation and patent ductus arteriosus were present and, curiously, also a murmur of the ductus type. No cyanosis of the feet could be detected on repeated examination. Resection of the aorta with ligation of the ductus was advised and this was carried out by Dr O T Clagett of the Division of Surgery. Unfortunately, the child died fourteen days postoperatively from complications. The heart weighed 250 gm, compared to a predicted normal weight of 85 gm and the right ventricle was tremendously hypertrophied. It would appear that operation in such cases as this should be performed as early as technically possible as it is doubtful that such a heart as this child had could ever have returned to normal.

The natural history of a patent ductus arteriosus may proceed in various ways. The question whether a ductus arteriosus may spontaneously close after being patent for some months or years cannot be definitely answered. There are isolated clinical reports^{11 12} that strongly indicate that the ductus may close after the first year of life but there is a paucity of histologic evidence to substantiate such a view. In a recent case at the Clinic in which operation was done at 3 years of age because of increasing cardiac enlargement, ductus tissue was examined by Edwards⁹ who concluded that the histologic appearance strongly suggested progressive closure. Sufficient evidence of the possibility of late spon-

taneous closure is available to indicate that operation should not be undertaken as a purely elective procedure until the fourth year or later. Even when a pressure gradient which might be thought to favor maintenance of the patency of a ductus exists, as in pulmonary stenosis, clinical observations would indicate that the ductus may close in the later months of infancy. Such spontaneous closure seems the best explanation of the delayed appearance of cyanosis in many cases of tetralogy of Fallot, including the historic case of Sandifort described in 1777.²

While, in contrast to spontaneous closure of the ductus arteriosus, it is not feasible to speak of enlarging of the ductus, there seems to be occasionally an acquired alteration which would favor increased flow, and that is shortening of the ductus. If the pressure gradient and internal diameter of the ductus were kept constant and turbulence effects were disregarded, the flow should be inversely proportional to the length of the ductus. In some patients the ductus may be represented only by a circular fistula between the aorta and the proximal part of the left pulmonary artery, a lesion which has been called "window ductus." The technical difficulties of surgically closing such a ductus are obvious. This type of ductus has been observed only once in 21 cases in which autopsy was performed at the Clinic⁷ but occurred in 10 of the 60 fatal cases reviewed by Keys and Shapiro. To illustrate the lesion, a figure from von Rokitsky's book is reproduced (fig. 127).

The late effects of a patent ductus arteriosus are rather frequently related to the development of pulmonary vascular changes. The changes may sometimes be grossly evident in dilated atherosclerotic large arteries or they may be found only in the form of obstructive arteriolar and small artery lesions. Aneurysmal dilatation of the ductus itself is exceedingly rare. Reports concerning saccular aneurysms of a large branch of the pulmonary artery are also rare but such lesions characteristically are associated with a patent ductus arteriosus. Indeed, if a saccular aneurysm of a large pulmonary artery is diagnosed in a young nonsyphilitic adult, a patent ductus arteriosus, from a practical standpoint, may be assumed to be present.³

The syndrome of pulmonary hypertension due to a patent ductus arteriosus and obstructive pulmonary vascular lesions has been discussed by Douglas and co-workers.³ The probability that a true "cyanosis tardive" can occur owing to reversal of flow in the ductus should be accepted, but definite proof is lacking. Such proof may be forthcoming if a patient with a patent ductus arteriosus is found in whom the pressure



Fig. 127.—Fistulous or window type of ductus arteriosus (a) The patient was 23 years of age and died from congestive heart failure associated with cyanosis. A continuous murmur had been noted in the clinical records. (From von Rokitsansky, Carl, *Ueber einige der wichtigsten Krankheiten der Arterien*, Wien: Staatsdruckerei, 1852, 72 pp.)

in the pulmonary artery exceeds that in the systemic artery and whose arterial oxygen saturation is subnormal, especially if the saturation level in the sample from the femoral artery is lower than that of the sample from the right radial artery. It may be emphasized that reversal of flow might be considerable without recognizable cyanosis, this clinical sign being absent with significant degrees of arterial desaturation. As a commentary on the effect of tradition in medicine, it is odd that there is the tendency to use cyanosis as a clinical indication of subnormal arterial hemoglobin unsaturation in

congenital heart disease in spite of the fact that the unreliability of blueness as an indication of arterial hypoxemia has been emphasized to hundreds of flight surgeons and thousands of flying personnel

Another lesion of the pulmonary artery is subacute bacterial endarteritis in which pulmonary symptoms and signs may sometimes dominate the clinical picture. There is some difference of opinion as to the proper time for surgical treatment. From the internists' point of view, it would seem better, if the infecting organism is penicillin-sensitive, to treat the two conditions separately, treating the infection like subacute bacterial endocarditis, then later giving surgical treatment for the ductus. The ultimate answer to the problem will have to come from the surgeon, the answer depending upon whether an actively infected ductus and the general effects of the infection on the patient or scarred ductus and periductal tissue constitutes the greater risk. Undoubtedly, lesions recognized very early may be subjected to surgical treatment early, in cases in which the diagnosis is made late, considerable preoperative therapy is indicated. Until the surgical technical difficulties can be further determined, the situation is much as analyzed by Vessel and Kross ¹⁸

In contrast to the clinical course of patency of the ductus arteriosus in relation to pulmonary hypertension and pulmonary vascular changes, there may occur only evidence of prolonged work load on the left ventricle, with progressive dilatation and hypertrophy of this chamber. In such instances as this, the heart on postmortem examination resembles the heart of hypertension and if the great vessels are not available for examination one cannot make the distinction. An inquiry into the possibility that in some instances a large left ventricle may decrease in size, consequent to the decreased output that results from the decreased ductus flow related to the development of pulmonary hypertension and a reduced aortic-pulmonary pressure gradient, leads mainly to conjecture. Over a period of fifteen years in 1 patient the electrocardiographic examination gave evidence which varied from that which suggested left ventricular enlargement to that which strongly indicated right ventricular hypertrophy ⁷

Such evidence is far from conclusive. The left ventricular endocardial fibrosis noted in 1 case has also been presented as some evidence that the left ventricle at one time was larger than in the later years of life.⁴ It is known, however, that a greatly enlarged left ventricle that is related to a patent ductus arteriosus sometimes may not return to normal size after surgical cure of the ductus. In a patient who was studied by Dry and co-workers⁶ and who died suddenly four and a half years after successful obliteration of a ductus, the left ventricle was still greatly dilated and hypertrophied. The reversibility of heart disease as related to the removal of the etiologic factor has very definite limitations.

Two cases have been chosen to illustrate clinical problems the solution of which is not completely evident.

ILLUSTRATIVE CASES

CASE 1—An infant born a few weeks prematurely weighed 5 pounds (2.3 kg.). A loud basal systolic murmur was noted on the day of birth and cardiac enlargement was evident in the roentgenogram made on the third day (fig. 128). No cyanosis was ever present and the murmur remained the same in numerous examinations throughout the period of forty-two days the child lived. Congenital cataracts were present but there were no other anomalies. *There was no history of maternal illness in the first trimester of pregnancy.* The child was brought back to the hospital because of a feeding problem and died suddenly.

On postmortem examination the heart weighed 34 gm., which was approximately twice the predicted normal weight, and there was a widely patent thin walled ductus arteriosus (fig. 128d). Under the right anterior aortic cusp was an aneurysmal bulging of the membranous portion of the ventricular septum but no opening. There was a small slitlike patency of the foramen ovale. Proximal to the ductus the aorta showed the normal degree of narrowing that is seen in young infants. The coronary vessels arose from the aorta in a normal manner, and histologic examination of the myocardium revealed no abnormality.

From the pathologic viewpoint the child in the preceding case died from a patent ductus arteriosus but the exact reasons remain unknown. The very early cardiac enlargement suggests that this enlargement might have begun in intra uterine life. In congenital heart disease the various factors that seem responsible for cardiac hypertrophy are obstructions of the

aortic or pulmonary orifices, greatly increased output of either one or both ventricles through recirculation of blood in one or both systems, and extremely low oxygen tension of the coronary blood. Since, on histologic study of the lungs, there was no evidence of pulmonary vascular abnormality

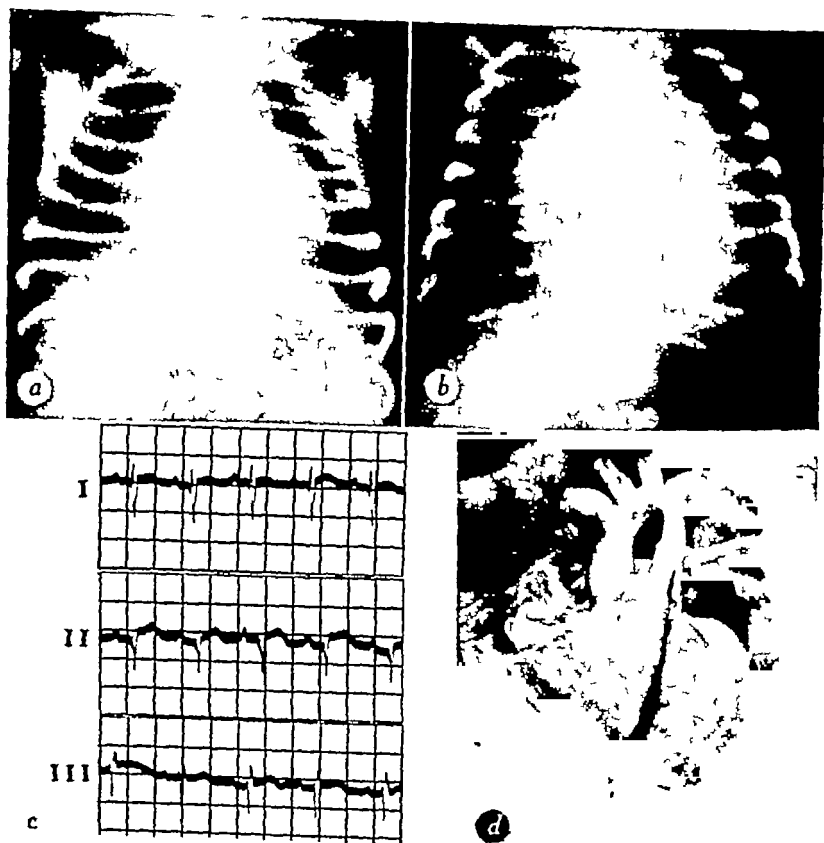


Fig 128 (Case 1) —Roentgenograms made on, *a*, the third day, and *b*, the thirtieth day after birth showing the generalized and progressive cardiac enlargement *c*, Electrocardiogram made on the fifth postnatal day *d*, Gross specimen showing the patent ductus arteriosus and enlargement of both ventricles of the heart

and since the two ventricles were of equal size and the foramen ovale had normal slitlike patency, it may be assumed that the fetal circulation was normal in type. It seems most unlikely that the fetal placental blood flow was inadequate and caused only cardiac hypertrophy. The best explanation seems to be that acute heart failure resulted from persistent patency of the ductus arteriosus in a manner similar to that in which

rapid heart failure occurs in animals with large experimentally produced arteriovenous fistulas. How such a condition as occurred in this case could be diagnosed with sufficient accuracy, at the age at which the patient was seen, to justify reference for surgical therapy is a difficult problem. It may be mentioned that persistent patency of the ductus arteriosus seems uniquely common among the defects of the heart following maternal rubella¹⁷ and such an association might be suggestive clinically of the diagnosis. The infant was premature but there is no evidence that prematurity of birth itself favors persistent patency of the ductus arteriosus.¹

CASE 2—A boy aged 9 years had been referred to a university center some years previously with a diagnosis of patent ductus arteriosus. The clinical diagnosis apparently had been agreed upon but the parents decided against operation because of the risk, as the child was completely asymptomatic. At the time of his examination at the Clinic, there was no continuous murmur and no collapsing pulse. A basal systolic murmur of moderate intensity was present and a faint, early diastolic murmur was heard intermittently. The blood pressure was 100 systolic and 50 diastolic expressed in millimeters of mercury. The electrocardiogram showed right axis deviation. Roentgenologic study revealed a prominent shadow of the pulmonary artery and increased hilar pulsations (fig. 129). It was suspected clinically that the child had an atrial septal defect. Cardiac catheterization revealed pulmonary hypertension and arterialization of the venous blood above the pulmonary valve. On this evidence the diagnosis of ductus arteriosus was made (table 1).

In the preceding case the ductus flow was small compared to that frequently found by Eppinger and co-workers¹⁰ but it was of considerable magnitude in view of the slight gradient of pressure across the ductus and the age of the child. That pressure in the pulmonary artery may be normal in the presence of a large ductus has been confirmed in unpublished pre-operative cardiac catheterization studies made in the Clinic cardiovascular laboratories under the direction of Dr. Earl Wood.

The preceding cases emphasize that the murmur of a patent ductus may be only systolic in time and rather non-specific in nature. This seems particularly true in infants.

young children Gross has mentioned that he has not operated upon anyone with right axis deviation, however, as emphasized by the last case, this criterion for diagnosis should not be absolute. All patients who have atypical lesions will need special investigation by means of catheterization of the right side of the heart to establish the diagnosis with sufficient

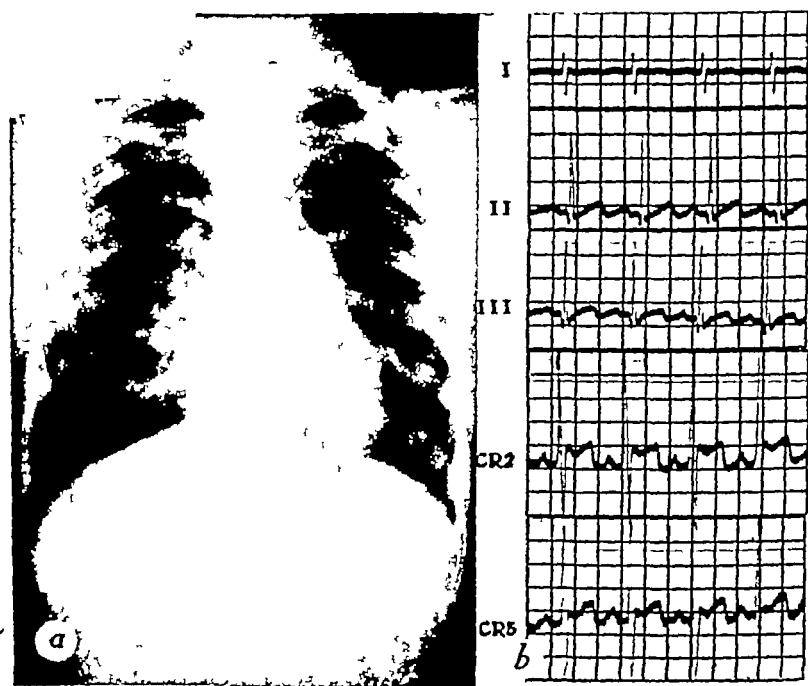


Fig 129 (Case 2) —a, Note the prominent shadow of the pulmonary artery and hilar markings b, Right axis deviation is shown

certainly to justify surgical treatment, the lesions usually to be excluded being atrial and ventricular septal defects

If a patent ductus arteriosus should be found to exist along with an intracardiac lesion it is generally considered non-surgical, but with an associated small ventricular or auricular septal defect, surgical treatment of the ductus should be undertaken if the arterial blood is normally saturated with oxygen, if it retains normal saturation with exercise and if catheterization of the pulmonary artery has been readily accomplished

Dexter and co-workers⁴ were among the first to emphasize the diagnostic value of catheterization of the right side of the

heart in congenital heart disease. When technically successful this method has given a relatively exact method of determining the nature of congenital cardiac defects, which together with angiocardiology, is an improvement on the previous methods of comparing cases on the basis of reasoning and statistical probabilities.

TABLE 1
ESSENTIAL DATA OBTAINED ON CARDIAC CATHETERIZATION IN CASE 2*

	Oxygen Saturation per cent	Pressure mm. of mercury	
		Systolic	Diastolic
Right auricle	64	8	1
Right ventricle	68	108	10
Left pulmonary artery	83	108	61
Right pulmonary artery	77	113	59

Calculated volume of ductus flow 2.31 liters per minute (approximately half that of left ventricular output)

* The difference in oxygen content of right auricle and right ventricle is of borderline significance technically but it was a consistent finding in 2 samplings taken from each chamber thus indicating a slight pulmonary insufficiency. The finding is consistent with the first clinical interpretation of the soft diastolic murmur that was heard. The oxygen difference between the 2 pulmonary arteries amounting to 1.3 volumes per cent, is quite significant and if the oxygen content of the blood in the left pulmonary artery were used calculation of the shunt would give a value approximately 15 per cent higher than when the mean of the contents of the 2 pulmonary arteries is used. The pressures were obtained by strain gauge manometers and photographic recording after the method of Lambert and Wood. Blood in the radial artery was 98 per cent saturated. The systemic pressure unfortunately was not measured during the period of the recording of the pressure in the pulmonary arteries.

CONCLUSIONS

While in the usual case of ductus arteriosus the clinical syndrome readily permits a diagnosis, in other cases an atypical picture is presented in which the development of pulmonary hypertension dominates the picture.

The characteristic continuous murmur may be absent in cases of patent ductus arteriosus particularly during infancy.

or after the development of pulmonary hypertension or in the presence of heart failure

Attention has been drawn to the irreversible changes that may occur in the pulmonary vascular tree or in a hypertrophied left ventricle which may limit the completeness of the surgical cure if surgical treatment has been long delayed

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ANOMALIES OF THE DERIVATIVES OF THE AORTIC ARCH SYSTEM

JESSE E EDWARDS

It is known that certain vascular anomalies resulting from maldevelopment of the derivatives of the aortic arch system may be responsible for symptoms resulting from compression of either the trachea or the esophagus. The symptoms, physical signs, roentgenographic features and surgical therapy have been the subjects of many articles. The symptoms vary considerably. In some instances no symptoms may be present during a full lifetime ^{2, 11, 23, 26, 4, 44}. In other instances symptoms may be noticed at birth or shortly thereafter ^{10, 16, 20, 26, 8, 41, 45, 51}. When they appear at this early time of life, manifestations of respiratory involvement usually overshadow those of esophageal malfunction, although the reverse may be true ²¹. In the newborn symptoms include cough, inspiratory and expiratory stridor, intercostal and suprasternal retraction with inspiration and attacks of cyanosis which may be precipitated by ingestion of food. Regurgitation may follow ingestion of food, and drinking may be associated with apparent discomfort. There is a tendency toward pulmonary infection. The symptoms cited are sometimes attributed to an enlarged thymus and since roentgenographic examination of the thorax may reveal a widened mediastinal shadow, consistent with an enlarged thymus, the initial impression may be that an enlarged thymus is the basis for the infant's difficulties. So strongly may the diagnosis of enlarged thymus be entertained that it is not uncommon for radiation to be applied in an effort to shrink the thymus. This proves of no avail. Unless surgical measures are employed to correct those vascular anomalies causing pronounced symptoms, it is common for the infant to die of pulmonary infection.

The clinical impression that some sort of vascular anomaly is responsible for the symptoms may be gained from bronchoscopic examination which may reveal a zone of tracheal narrowing. It is usually simpler and more advisable to administer a small amount of barium and to visualize the esophagus roentgenographically. A zone of constriction of the

esophagus in the upper thoracic region will usually be readily evident and will lead the physician to the correct interpretation as to the basis for the symptoms. If no symptoms occur during infancy, the patient may never suffer as a result of his vascular abnormality. On the other hand, symptoms may first become evident later in life.^{6,8 27,29 40 43} As a result of aging changes which cause dilatation of the aorta and its branches, anomalies which produced no symptoms during infancy or childhood may become troublesome during adult life, especially during advancing age. When symptoms first appear in adult life they are usually in the form of persistent cough, dysphagia and rarely, hoarseness.

The exact anatomic nature of the vascular anomaly can frequently be ascertained by the application of several roentgenographic technics and criteria. These have been described.^{3 4 6,17 18,20,29,33 34 40,42 43,45} It is not the purpose of this communication to consider these to any extent.

Knowledge concerning the configuration of the various anomalies of the aortic arch derivatives is important to the clinician, to the roentgenologist and to the surgeon who treat patients who have symptoms attributable to these anomalies. To the clinician and roentgenologist, this knowledge may be used to advantage in evaluating the findings in cases in which symptoms may result from the presence of vascular anomalies. To the surgeon, realization of the possible vascular configurations which may interfere with the function of either the esophagus or the trachea will serve as a guide, while exploring the region of the aortic arch, in determining the exact nature of the anomaly in a given case. This determination will serve to guide the surgeon to perform those procedures most suitable for the correction of the condition or for the relief of symptoms resulting from it.

The primary purpose of this communication is to describe and to illustrate* those anomalies of the derivatives of the

* I am indebted to Mr. Russell L. Drake for the preparation of the illustrations. It is to be emphasized that these are diagrammatic representations. At times it was necessary to make minor modifications of relations in order that the salient features of a given condition could be brought out in one illustration. For the preparation of the illustrations of those anomalies which have been reported, use has been made of the author's personal experience and of illus-

aortic arch system which may interfere with the function of either the esophagus or the trachea. The subjects of persistent patent ductus arteriosus and coarctation of the aorta are not included. The majority of the anomalous configurations to be presented have been described. To these will be added several configurations which, as far as the author knows, have not been reported. Yet these stand out as distinct possibilities. Consequently, they will be included as hypothetical forms. This is done with the hope that when they are encountered, they will be understood and not be viewed with undue surprise. Furthermore, it is hoped that whosoever observes these hypothetical possibilities will be stimulated to place them on record in order that the literature may contain a more comprehensive accumulation of this group of anomalies.

In discussions such as this it is customary to employ the standard Rathke diagram of the six aortic arches in explaining the developmental basis for the various aortic arch anomalies and in relating the various types to each other. While this approach is perfectly logical and correct, the reader, nevertheless, is likely to be somewhat confused. The reason for this is explained by several factors. Not only do a number of structures of the primitive aortic arch system disappear, but there are important alterations in the shape of the aortic arch pattern. This results from the fact that while some portions of the primitive arterial pattern grow in equal proportion to the growth of the body, other portions grow relatively little with respect to the growth of the body as a whole. This produces distortions of the basic diagram of six arches. Moreover there are important shifts in the relative situation of the subclavian arteries to that of the six aortic arches (ducti arteriosi). Thus in the basic diagram of the six aortic arches, which is customarily employed, the subclavian arteries lie caudad to the sixth arches. Yet by the time of birth important differences in the rates of growth of the portions of the aortic arch system result in the presence of the subclavian arteries in a cephalad position with respect to the sixth aortic arches.

I feel that a better understanding of the relationship of

trations in such works as those of Bayford, Quain, Turner, Abbott, Thomson, Holzappel, Kopsch, Poynter, Arkin, Wolman, Gross, and others.

the aortic arch anomalies, from a developmental point of view and with respect to each other, can be had by an approach other than the employment of the basic primitive and diagrammatic six arch pattern. It seems best to employ, as the basic pattern, an anomaly which, while it contains the essential features of the primitive aortic arch pattern, has as well gone through the growth adjustments that take place in all persons

For this reason, the anomaly known as the functioning double aortic arch is chosen as the basic pattern. To fulfill completely the line of reasoning, this anomaly should contain right and left ducti arteriosi but usually only one ductus arteriosus is present. The one adjustment that the reader must make is to realize that the functioning double aortic arch represents with one exception the primitive aortic arch pattern, in which growth adjustments have taken place. The one exception is that one of the sixth aortic arches has largely disappeared.

In my opinion, malformations of the aortic arch derivatives may be divided into two groups depending upon whether the ductus arteriosus* takes its origin from the left pulmonary artery or from the right pulmonary artery. Arbitrarily, in cases in which the ductus arteriosus arises from the left pulmonary artery the anomalies are classified under Group I while in cases in which the ductus arteriosus takes its origin from the right pulmonary artery the anomalies are placed in Group II. Group I is by far the larger of the two. Although exceptions to the rule occur, the upper portion of the descending aorta lies on that side of the body on which the ductus arteriosus is found.

In those cases in which the upper portion of the descending aorta lies on the right side, the lower portion of the descending aorta crosses to the left at about the level of the body of the eighth or ninth thoracic vertebra to leave the thorax through the aortic hiatus.

* The term "ductus arteriosus" will be used interchangeably with the term "ligamentum arteriosum." Patency of the ductus arteriosus is not an essential part of the anomalies to be considered although it may be encountered, additionally.

GROUP I LEFT-SIDED DUCTUS ARTERIOSUS AND LEFT-SIDED DESCENDING AORTA

A Functioning Double Aortic Arch—The double aortic arch has the following characteristics. The ascending aorta arises normally from the left ventricle and then divides into two arches, a left and a right. The left or so-called anterior arch follows closely the course of the normal aortic arch. It passes in front of the trachea and over the left major bronchus to join the descending aorta which lies on the left side of the body. The right or so-called posterior arch passes over the right major bronchus and then turns rather abruptly to the left behind the esophagus and in front of the vertebral column. It joins the left arch either to the left of or behind the esophagus at the point at which the latter arch joins the descending aorta. The branches of the aortic arches are symmetrically arranged. The right common carotid and the subclavian arteries arise independently in that order, from before backward, from the right aortic arch. Similarly, the left common carotid and subclavian arteries arise from the left arch. The ductus arteriosus is inserted into the left arch between the origin of the left subclavian artery, in front and the junction of the left and right arches, behind. The lower attachment of the ductus arteriosus is to the left pulmonary artery (fig. 130a).

It is evident that in the case of functioning double aortic arch the trachea and esophagus are encircled by a vascular ring composed of the bifurcation of the ascending aorta in front, the right and the left aortic arches laterally, and either the posterior limb of the right aortic arch alone or the junction of the two arches behind. If the vascular ring is sufficiently tight to compress the two tubes which it encircles the trachea is usually compressed at each side and is thus converted into a triangular-shaped tube at the level of the arches. The esophagus is compressed from behind forward. The connections of the ductus arteriosus are such as to hold the bifurcation of the pulmonary trunk tightly against the front of the trachea which increases the pressure of vessels against this tube.

This appears to be particularly true if the posterior junc-

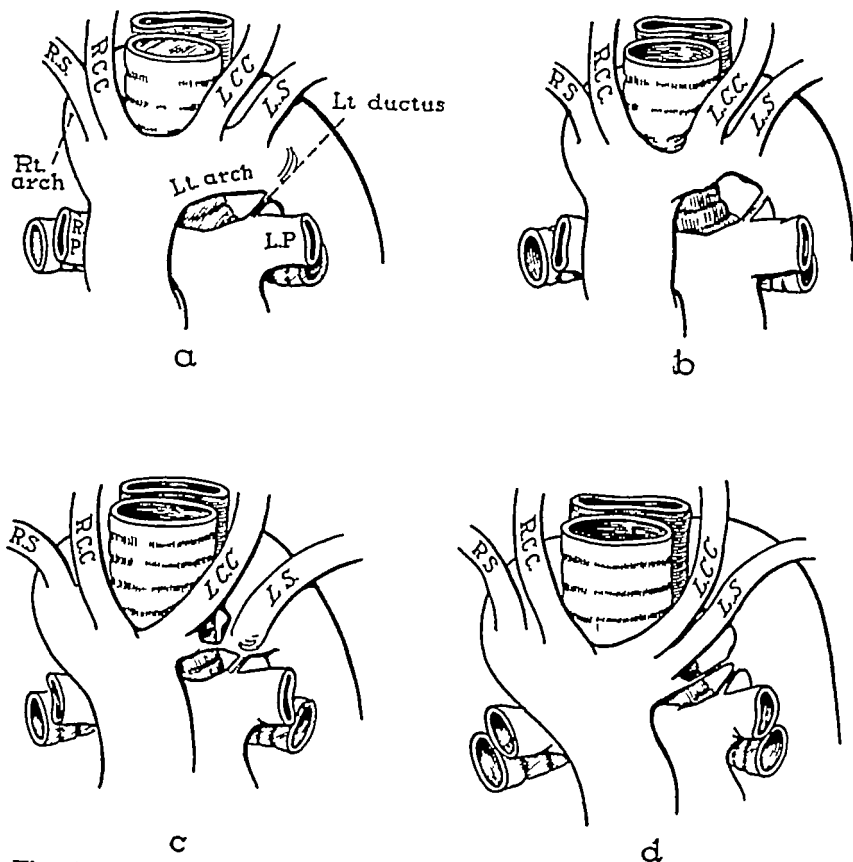


Fig 130—Left-Sided Ductus Arteriosus and Descending Aorta (Group I)
a Functioning Double Aortic Arch This is the basic pattern from which all the anomalies of Group I, shown in figures 130 and 131, are derived. In functioning double aortic arch, two arches are derived from the ascending aorta. The left pursues a course similar to that of the normal aortic arch. The right arch, after crossing over the right major bronchus, deviates to the left, behind the esophagus, to join the left arch and descending aorta to the left of the midline. Occasionally, this junction may be behind the esophagus. The trachea and esophagus are encircled by the aortic structures. The left-sided ductus arteriosus holds the left pulmonary artery and the bifurcation of the pulmonary trunk against the anterior surface of the trachea. The right and left arches are of approximately equal caliber.

b Functioning Double Aortic Arch The vascular pattern is identical to that in figure 130a. This is a more common form of functioning double arch. In it the left arch is the more narrow of the two.

c Partial Atresia of Double Aortic Arch In this anomaly the basic pattern shown in figure 130a is altered in such a way that there is a zone of atresia of the left aortic arch between the origin of the left common carotid artery and that of the left subclavian artery. Although there is no longer a functioning double arch, there is still a vascular ring about the esophagus and trachea, as in the functioning double aortic arch. This anomaly is hypothetical.

d Partial Atresia of Double Aortic Arch In contrast with figure 130c, the zone of atresia of the left aortic arch lies between the origin of the left subclavian artery and the aortic insertion of the ductus arteriosus.

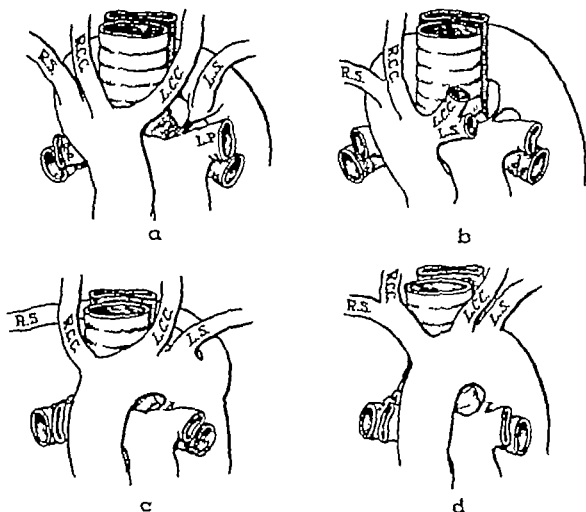


Fig 131—*Left-Sided Ductus Arteriosus and Left-Sided Descending Aorta (Group II)* a. *Right-Sided Aortic Arch with Retro-Esophageal Segment and Left Sided Descending Aorta Left Subclavian Artery Originating from Aortic Diverticulum.* In figure 130c there was illustrated a zone of atresia in the left portion of a double aortic arch. The zone lay between the origins of the left common carotid and subclavian arteries. In that type of anomaly the atresia would be expected to occur late in fetal life or after birth therefore the atretic segment would be still recognizable. If the atresia occurs in the same situation in early intra-uterine life the anomaly illustrated in this figure occurs. There is a right sided aortic arch with a retro-esophageal segment which joins the left-sided upper portion of the descending aorta. The left subclavian artery arises as the fourth branch of the aorta from a diverticulum to which the ductus arteriosus also is attached. The diverticulum represents the pervious most posterior part of a left aortic arch. There is a vascular ring about the trachea and esophagus; this ring is composed of the right aortic arch on the right, the retro-esophageal segment of the right aortic arch behind the aortic diverticulum and the ductus arteriosus on the left and the bifurcation of the pulmonary trunk in front.

b. *Right-Sided Aortic Arch with Retro-Esophageal Segment and Left-Sided Descending Aorta Left Subclavian Artery Originating from Left Innominate Artery.* This anomaly varies from that shown in figure 131a only in that the gap in the left aortic arch lies between the origin of the left subclavian artery and the aortic insertion of the ductus arteriosus. Consequently the left subclavian artery arises from a left-sided innominate artery. The ductus arteriosus is inserted into a remnant of the posterior portion of the left arch which usually appears in the form of an aortic diverticulum. As the anomaly shown in figure 131a is comparable with the one shown in figure 130c this anomaly is com-

tion of the left and right aortic arches is behind rather than to the left of the esophagus. In such instances there is greater tension upon the ductus arteriosus, which, in turn, tends to pull the bifurcation of the pulmonary trunk more firmly against the anterior surface of the trachea.

(c) When a functioning double aortic arch exists the two arches are often of unequal diameter, the right one usually is the wider⁸ (fig. 130b). Occasionally, the two arches may be of approximately equal caliber.¹⁰ I have personally observed an example of this. In still other instances, the left arch may be the larger of the two. This was the situation in the following case which was reported by Gordon (case 4).

The patient was a boy, five weeks of age, whose clinical history was characterized by noisy breathing which was intensified when the infant was lying down or was fed. Roentgenographic examination of the thorax revealed a wide mediastinal shadow which was first interpreted as a manifestation of an enlarged thymus. Bronchoscopy revealed a high-grade compression stenosis of the trachea, at the carina, and similar compression of both main bronchi. Roentgenologic examination of the esophagus with barium revealed esophageal compression. It was believed that a vascular malformation was responsible for the clinical features described. A left thoracotomy disclosed a left-sided ligamentum arteriosum. The aorta seemed to show a normal configuration, the left arch was of normal size and blended in a normal manner with the descending aorta, which was on the left side. A sudden attack of cyanosis occurred three days after the operation and the child died. Necropsy revealed a double aortic arch. The left arch was of normal size but the right arch was smaller.

parable with the one shown in 130d

c Left-Sided Aortic Arch and Left-Sided Descending Aorta, Right Subclavian Artery Arising from the Distal Arch or from the Upper Portion of the Descending Aorta. If the right portion of the double arch shown in figure 130a disappears between the points of origin of the right common carotid and right subclavian arteries, the pattern shown in this figure occurs. The right subclavian artery arises as the fourth branch of an otherwise normal aorta. The right subclavian artery passes in close relation to the esophagus as it proceeds to the right side of the body and may compress that tube. The artery usually passes behind the esophagus.

d Left-Sided Aortic Arch and Left-Sided Descending Aorta (Normal Pattern). If that portion of the double arch illustrated in figure 130a disappears posterior to the origin of the right subclavian artery, the right subclavian artery arises from the innominate artery. A normal vascular pattern is then produced.

In cases of double aortic arch, the left arch usually is the smaller of the two but the case reported by Gordon proves that this does not always hold true. The two arches may be of equal size or the right arch may be the smaller of the two.

B Partial Atresia of One Aortic Arch—An accentuation of the inequality of the two aortic arches leads to anomalies in which part of one of the arches is atretic and resembles a fibrous cord. As a rule, the atresia is situated in the left arch but it is a hypothetical possibility that portions of the right arch, instead, may be atretic. In general three anatomic forms may represent this subgroup, depending upon the site of the atretic segment of the left arch. Hypothetically, the atresia may involve that part of the left aortic arch which lies between the origins of the left common carotid artery and the left subclavian artery (fig. 130c), it usually lies between the origin of the left subclavian artery and the aortic insertion of the ductus arteriosus^{3 7 9 16 47} (fig. 130d) or it may involve the most distal part of the left arch, between the aortic insertion of the ductus arteriosus and the region of the posterior junction of the left and right aortic arches.⁵⁰ In any of the varieties of partial atresia of a double aortic arch the trachea and esophagus are encircled by a vascular ring, partly atretic, and, if the ring is sufficiently narrow, compression effects upon these structures are identical to those produced by a narrow vascular collar caused by a double aortic arch in which the two arches are pervious.

C Right-Sided Aortic Arch with Retro-esophageal Segment and Left-Sided Descending Aorta—In cases of double aortic arch in which a portion of one arch is atretic but recognizable, it is evident that the atresia occurred rather late during fetal life or after birth. Should the process of obliteration of a portion of a double aortic arch occur relatively early in fetal life, it is possible that the atretic segment would no longer be present as an identifiable structure at the time of birth. The double arch would cease to exist as a continuous structure. Such variants of the double aortic arch are included in the next subgroups.

1 *Right Sided Aortic Arch with Retro-esophageal Segment and Left Sided Descending Aorta. Left Subclavian Artery Origin*

nating from Aortic Diverticulum —If that segment of the left aortic arch between the origin of the left common carotid artery and left subclavian artery disappears, the following aortic arch pattern is achieved (fig 131a) There is but one complete aortic arch, the right, which after passing over the right bronchus, turns to the left, at about the level of the body of the third or fourth thoracic vertebra, between the esophagus in front and the spinal column behind Either directly behind the esophagus or to its left, the aortic arch joins the descending aorta, which usually lies to the left of the midline The first three branches of the aortic arch are the left common carotid, the right common carotid and the right subclavian arteries in that order from before backward The left subclavian artery arises as a fourth branch of the aorta from a diverticulum-like outpouching that lies at the left upper angle of the junction of the right aortic arch with the descending aorta The diverticulum usually lies against the left side of the esophagus and into its lower anterior aspect is inserted the upper portion of the ductus arteriosus The lower attachment of the ductus arteriosus is to the left pulmonary artery ^{7,15 27,36 38,39,47 49}

This condition is comparable with that illustrated in figure 130c, in which there was predicted atresia of that segment of the left aortic arch between the origins of the left common carotid and left subclavian arteries In that condition, the atretic segment would be identifiable as a fibrous-like cord. In the condition under this heading, the atretic segment is no longer identifiable, therefore, on casual examination, one might not identify the anomaly as a variant of the double aortic arch which, however, it should be considered to be The aortic diverticulum which gives rise to the left subclavian artery and which is a point of attachment for the ductus arteriosus should be interpreted as a patent posterior portion of a left aortic arch The segment of the left aortic arch between the origin of the left subclavian and common carotid arteries has disappeared during early embryonic life and is not identifiable

In certain instances, the aortic diverticulum has approximately the same diameter as the subclavian artery to which

it gives origin. Under such conditions, the diverticulum appears as the proximal part of the left subclavian artery, and the ductus arteriosus which actually is attached to the diverticulum appears to be attached to the beginning of the left subclavian artery.^{2,24} Such variations in gross appearance do not alter the basic concepts concerning the significance of the vascular pattern. Rather they represent minor variations in relative rates of growth.

While there is absence of the symmetrically constricting effects of a continuous double aortic arch, there is, nevertheless, a vascular ring about the trachea in anomalies of this subgroup. The ring is formed by the right aortic arch on the right, the retro-esophageal segment of the right aortic arch behind, the aortic diverticulum and the ductus arteriosus on the left, and the bifurcation of the pulmonary trunk in front. The subclavian artery plays no role in forming the vascular ring. In such instances a break in the continuity of the vascular ring may be accomplished by the division of the ductus arteriosus, which allows left lateral expansion of the trachea and the esophagus. The procedure also allows the bifurcation of the pulmonary trunk to sag away from the front of the trachea with relief of pressure against that tube. In addition, Gross in discussing this type of anomaly stressed the possibility of compression of the trachea by the left common carotid artery which arises to the right of the midline and crosses in front of the trachea to achieve its usual position on the left side of the superior mediastinum. He recommended dislocating this vessel from its close association with the trachea if it compresses the air passage unduly.²

2 *Right-Sided Aortic Arch with Retro-esophageal Segment and Left-Sided Descending Aorta, Left Subclavian Artery Originating from Left Innominate Artery*—Referring to the double aortic arch (fig. 130a), it is evident that if the portion of the left aortic arch between the origin of the left subclavian artery and the insertion of the ductus arteriosus disappears, the aortic arch pattern appears as follows (fig. 131b). There is one aortic arch, the right. This passes over the right major bronchus after which it turns to the left, passes between the esophagus and the spinal column, as in the other anomalies

previously described Behind, or to the left of the esophagus, it joins the left-sided descending aorta As in Group C-1 there is a diverticulum at the junction of the aortic arch and descending aorta ^{3,24} The ductus arteriosus is inserted into this diverticulum The left subclavian artery does not arise from the diverticulum but instead arises from a left-sided innominate artery in common with the left common carotid artery The left innominate artery is the first branch of the aortic arch, the second and third branches being the right common carotid and right subclavian arteries, respectively

As in Group C-1, there is a constricting vascular ring about the trachea and the esophagus It is to be remembered that the aortic insertion of the ductus arteriosus is actually to a remnant of the most posterior portion of the left aortic arch and that this diverticulum is shorter than it is in the comparable anomaly in which the left subclavian artery arises from an aortic diverticulum Consequently, in the type of anomaly described in this section, the diverticulum is expected to be small and it often is Moreover, on the basis of molding of vessels with growth, it is possible for a diverticulum not to be immediately apparent It is to be remembered, however, that the aortic insertion of the ductus arteriosus is to tissue which must be considered tissue of the left aortic arch

D Left-Sided Aortic Arch and Left-Sided Descending Aorta.—The types of anomalies that have been considered thus far were characterized not only by the presence of the ductus arteriosus on the left side but also by the presence of a right-sided aortic arch either alone or associated with a left-sided aortic arch Since the upper part of the descending aorta lay either in the midline or to the left of the midline, the posterior portion of the right aortic arch possessed a horizontal segment, behind the esophagus, which was directed toward the descending aorta In the remaining two types of vascular patterns to be considered in Group I, the left aortic arch is the only one that is present as a continuous functioning vessel Portions of the right arch have disappeared

1 *Left-Sided Aortic Arch and Left-Sided Descending Aorta, Right Subclavian Artery Arising from Distal Portion of Aortic Arch or from the Descending Aorta*—This aortic arch pattern

is characterized by the disappearance of the segment of the right portion of the double aortic arch between the origins of the right common carotid and the right subclavian arteries. Consequently, the first branch of an otherwise normal left-sided aortic arch is the right common carotid artery rather than the innominate artery. The second and third branches of the arch are the left common carotid and the left subclavian arteries, respectively. The right subclavian artery arises as the fourth branch of the aorta from either the aortic arch or the upper part of the descending aorta (fig 131c). The origin of this artery is frequently wider than the rest of the intrathoracic portion of the vessel, a feature that is not surprising since the origin of the right subclavian artery in this anomaly represents the most posterior portion of a right-sided aortic arch. From its origin on the left side of the midline the right subclavian artery proceeds upward and to the right in an oblique direction. It crosses the midline usually by passing between the esophagus, in front and the spina column behind. Less often, the artery lies between the esophagus and the trachea as it passes from the left side of the body to the right side, and even less commonly does it cross in front of the trachea.^{12 19 20 27 48} This type of anomaly of the aortic arch is the one most frequently observed, and as a rule, it does not give rise to symptoms. When the right subclavian artery arises as the fourth branch of the aortic arch and is responsible for symptoms, the symptoms usually result from esophageal compression and appear in the form of dysphagia.

2 *Left-Sided Aortic Arch and Left-Sided Descending Aorta Normal Arch and Branches*—It seems logical to include the features of the normal aorta at this point in the consideration since it too can be visualized as a modification of the double aortic arch. If one assumes that the double aortic arch is modified in such a way that there is loss of the right arch between the origin of the right subclavian artery and the descending aorta, one arrives at the structure of the normal aorta (fig 131d).

Under these circumstances, the first branch of the aortic arch is the innominate artery which soon divides into the

right common carotid and right subclavian arteries. The second branch is the left common carotid artery and the third is the left subclavian artery. The descending aorta lies on the left side and no undue compression upon the trachea or the esophagus is caused by the aortic arch or its branches. The ductus arteriosus extends from the left pulmonary artery to the aorta at a point beyond the origin of the left subclavian artery.

GROUP II RIGHT-SIDED DUCTUS ARTERIOSUS WITH UPPER PORTION OF DESCENDING AORTA ON THE RIGHT SIDE

The second group of anomalies of the derivatives of the aortic arch system is characterized by the ductus arteriosus being a right-sided structure and extending from the right pulmonary artery, below, to the aorta, above.

The upper portion of the descending aorta lies in the right side of the thorax, to the right of the esophagus. In the lower part of the thorax, usually at the level of either the body of the eighth or ninth thoracic vertebra, the aorta crosses to the left behind the esophagus and then emerges from the thorax through the aortic hiatus of the diaphragm.

In this group, the anomalies of the aortic arch, its branches and the upper portion of the descending aorta are essentially mirror images of the various anomalies of the first group. Anomalies of Group II are encountered less frequently than those of Group I but the counterparts of all the types in the first group have either been observed or exist as hypothetical possibilities in Group II.

A Functioning Double Aortic Arch.—As far as I have been able to determine, there is no case on record which fulfills all the criteria of the functioning double arch of Group II, yet this anomaly must be considered as a hypothetical possibility. Reference will be made, after the description, to two reported cases in which some of the features conform to those of the vascular structure which will be described.

In this type, the aortic arch divides into two arches, a right and a left. The right arch passes in front of the trachea and over the right major bronchus to join the descending aorta, which is on the right side of the body. The left arch passes

over the left major bronchus and then passes behind the esophagus to the right to join the right arch at the point at which it becomes continuous with the descending aorta (fig 132a) The upper portion of the descending aorta lies to the right of the midline As in its counterpart of Group I, the branches of the double arch of this group, the common carotid and subclavian arteries arise in that order from before backward from the arch of the respective side The ductus arteriosus arises from the right pulmonary artery and is inserted into the right aortic arch between the origin of the right subclavian artery and the posterior junction of the two aortic arches

The second case in the report of Sweet, Findlay and Reyersbach fulfills the aortic arch pattern of this anomaly but the matter of the site of the ductus arteriosus is problematic. The case history is interesting and instructive, not only from the diagnostic but also from the surgical points of view

The patient, a boy aged 4 years, had a cough that was associated with wheezing shortly after birth There were numerous attacks of pulmonary infection and dysphagia At the age of 4 years, he was able to eat only liquids or strained foods and vomited these There was evidence of esophageal and tracheal obstruction on roentgenographic examination A left-sided thoracotomy was performed At operation it was observed that the left arch assumed an unusual course Instead of remaining on the left side of the body as it does in the double aortic arch of Group I the left arch, after crossing over the left major bronchus deviated to the right and crossed the midline behind the esophagus The opening in the left side of the thorax was closed and a right thoracotomy was performed about three weeks later This procedure revealed that the right arch which had a diameter an eighth as large as that of the left arch passed over the right main bronchus which it compressed, and then became continuous with the descending aorta the upper portion of which was on the right side The left arch, after passing behind the esophagus reached the right side of the body and joined the right arch at the point at which the latter joined

the descending aorta The descending aorta remained on the right side of the body until it reached the lower portion of the thorax, where it deviated toward the midline Division of the right arch resulted in disappearance of symptoms The features of the aortic arch conformed to that illustrated in figure 132b

One major problem in this case, however, is the matter of the ductus arteriosus The authors said that at the operations they made a search for a ductus arteriosus on the left and the right sides but found none They concluded, therefore, that none was present and assumed that in the absence of a ductus arteriosus, the fetal circulation was balanced by either a defect in the atrial or ventricular septum and that such a defect closed shortly after birth, which explained the absence of clinical signs of a septal defect It is doubtful that such an assumption is correct It is more reasonable to assume that a ductus arteriosus was in fact present but was not discovered at the time of operation When one considers the rather intricate dissection necessary to find a closed right-sided ductus arteriosus, when present under ideal conditions at necropsy, it is understandable that one might be overlooked, even after a search was made for it, at operation If one assumes that a right-sided ductus arteriosus was not present in this case, the essential features of the double aortic arch of Group II would be fulfilled Since proof of the existence of a right-sided ductus arteriosus is lacking in the case cited the functioning double aortic arch of Group II must remain, for the time being, as a hypothetical anomaly It is interesting to contrast the aortic arch configuration in this case with the findings in the fourth case in the report of Gordon, to which reference has herein been made In each case there was a double aortic arch and the right arch was more narrow than the left In Gordon's case the anomaly definitely belongs to Group I since it was the right arch that passed behind the esophagus to join a left-sided descending aorta and the ductus arteriosus lay on the left side In the second case in the report by Sweet, Findlay and Reyersbach, the presence of the upper descending aorta on the right side coupled with the fact that the left arch was the one that crossed the midline behind the esophagus created

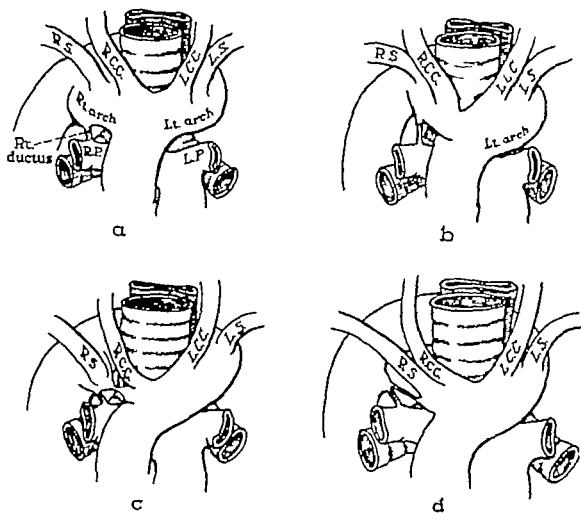


Fig 132 —*Right-Sided Ductus Arteriosus with Upper Portion of Descending Aorta on the Right Side (Group II)* The aortic arches, the ductus arteriosus and upper part of the descending aorta in the anomalies of Group II illustrated in figures 132 and 133 are mirror images of the vascular patterns of Group I which are illustrated in corresponding portions of figures 130 and 131

a. Functioning Double Aortic Arch The difference from the pattern illustrated in figure 130a lies in the fact that it is the left arch that passes behind the esophagus in this anomaly the ductus arteriosus and the upper portion of the descending aorta lie on the right side. As the anomaly shown in figure 130a is the basic type of Group I the one here illustrated is the basic pattern for Group II This is as yet a hypothetical anomaly

b. Functioning Double Aortic Arch In Group I the left arch is usually the more narrow of the two In this pattern which to date is a hypothetical one the right arch is expected to be the more narrow of the two

c. Partial Atresia of Double Aortic Arch To fulfill the mirror image of the anomaly illustrated in figure 130c the atretic segment lies in the right arch between the origins of the right common carotid and right subclavian arteries This is a hypothetical form.

d. Partial Atresia of Double Aortic Arch The mirror image of the pattern shown in figure 130d is illustrated The atretic segment lies in that portion of the right arch between the origin of the right subclavian artery and the aortic insertion of the ductus arteriosus. This form is hypothetical.

an aortic arch pattern different from that in Gordon's case and similar to the anomalies of Group II

B Double Aortic Arch with Atresia of One of the Arches.—As far as I have been able to determine, there are no reported examples in Group II of a double aortic arch in which a portion of one arch is atretic. Such anomalies may be anticipated. They are illustrated in figure 132c and d. They are represented as the mirror images of those anomalies of Group I in which a portion of the left arch is atretic. It is to be expected that if examples of the group under consideration are found the atretic segment will have a greater chance of lying in the right arch. Under such circumstances, the anomaly would show an accentuation of the narrow state of the right arch such as is illustrated in figure 132b. Support of the idea that one should expect to find in Group II examples of double aortic arch with an atretic portion of one arch exists from the fact that there are examples in which part of the right arch has disappeared completely. These are described in the next subgroup.

C Left-Sided Aortic Arch with Retro-Esophageal Segment and Upper Portion of the Descending Aorta on the Right Side.—1 *Right Subclavian Artery Originating from Aortic Diverticulum*—This aortic arch pattern (fig. 133a) is the mirror image of that member of Group I illustrated in figure 131a. This anomaly is rare but I recently reported a case in which it was present.¹⁴ When this type of anomaly is present, the appearance of the aortic arch system is as follows. There is only one complete aortic arch, that is, the left. After passing over the left major bronchus the arch turns to the right to cross the midline behind the esophagus. After it reaches the right side of the thorax it joins the descending aorta, the upper portion of which is also on the right side. At the right upper angle of the junction of the arch and descending aorta there is a diverticulum which lies along the right side of the esophagus. The right-sided ductus arteriosus is inserted into the lower anterior aspect of the diverticulum. The right subclavian artery is the fourth branch of the aortic arch arising from the upper aspect of the aortic diverticulum. The first three branches of the aorta are the right common

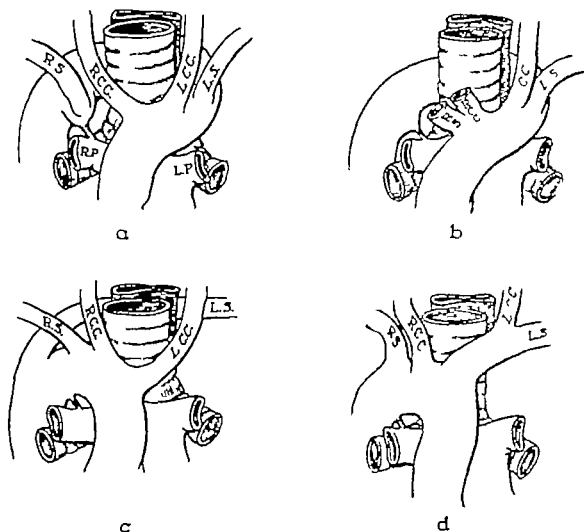


Fig 133 — *Right-Sided Ductus Arteriosus with Upper Portion of Descending Aorta on the Right Side (Group II)* a. *Left-Sided Aortic Arch with Retro-Esophageal Segment and Upper Portion of Descending Aorta on the Right Side* Right Subclavian Artery Originating from Aortic Diverticulum If that portion of the double aortic arch of Group II which is illustrated in figure 132a disappears between the points of origin of the right common carotid and right subclavian arteries, this anomaly occurs. There is a vascular ring about the trachea and the esophagus which is formed by the aortic arch on the left, by the retro-esophageal portion of the aortic arch behind by the aortic diverticulum and the ductus arteriosus on the right, and by the bifurcation of the pulmonary trunk in front. The aortic diverticulum represents the patent posterior portion of the right arch. The form illustrated is the mirror image of the anomaly illustrated in figure 131a

b. *Left-Sided Aortic Arch with Retro-Esophageal Segment and Upper Portion of Descending Aorta on the Right Side* Right Subclavian Artery Originating from the Right Innominate Artery This form varies from that shown in figure 133a only in that the portion of the right arch between the origin of the right subclavian artery and the aortic insertion of the ductus arteriosus has disappeared. This form is a mirror image of that illustrated in figure 131b

c. *Right-Sided Aortic Arch with Upper Part of Descending Aorta on the Right Side* Left Subclavian Artery Originating from the Aortic Arch or from the Descending Aorta This form may result from modification of the double aortic arch illustrated in figure 132a) in such a way that that portion of the left arch between the origins of the left common carotid and left subclavian arteries

carotid, the left common carotid and the left subclavian arteries in that order from before backward. As in its counterpart in Group I, this pattern is characterized by a vascular ring surrounding the trachea and the esophagus. Should symptoms result from this ring, division of the ductus arteriosus by means of a right thoracotomy would be indicated. It is of interest that the right common carotid artery arises to the left of the midline and crosses this line to get to its definitive position. In its course the artery may compress the trachea, and should symptoms result from this factor, dislocation of the artery might be helpful. Gross has advocated this procedure for the left common carotid artery in the condition which is the mirror image of the one under consideration.²²

The configuration of this type of anomaly may be understood if one studies the illustration of functioning double aortic arch in figure 132a. If one assumes that that part of the right arch between the origin of the right common carotid and right subclavian arteries disappears, one immediately recognizes the anomaly which is shown in figure 133a. The diverticulum to which the ductus arteriosus is attached and from which the right subclavian artery arises represents the patent posterior extremity of the right arch.

2 *Left-Sided Aortic Arch with Retro-Esophageal Segment and Upper Portion of Descending Aorta on the Right Side, Right Subclavian Artery Originating from a Right-Sided Innominate Artery*—If one assumes that a double aortic arch of Group II is altered in such a way that that segment of the right arch between the origin of the right subclavian artery and the right-sided ductus arteriosus disappears, the arterial configuration representative of this anomaly is obtained (fig. 133b).

disappears. The end result is a mirror image of the anomaly illustrated in figure 131c.

d *Right-Sided Aortic Arch with Upper Portion of Descending Aorta on the Right Side, Branches Forming a Mirror Image of the Normal Branches*. If that portion of the left aortic arch illustrated in figure 132a disappears posterior to the point of origin of the left subclavian artery, the latter vessel arises in common with the left common carotid artery from a left-sided innominate artery. The pattern is a mirror image of the normal, which is illustrated in figure 131d.

It varies from the type illustrated in figure 133a only in the mode of origin of the right subclavian artery. In the type already described, the subclavian artery arose as the fourth branch of the aorta from a diverticulum thereof. Inasmuch as the right arch is interrupted posterior to the subclavian artery in the anomaly now being considered the right subclavian artery arises in common with the right common carotid artery from the innominate artery. The ductus arteriosus is attached to an aortic diverticulum. This pattern is a mirror image of that member of Group I illustrated in figure 131b. At one time the anomaly under consideration remained as a hypothetical possibility but recently Paul has reported two cases in which the roentgenographic and surgical findings indicated the presence of an anomaly of this type. The configuration of the great vessels in these cases was identical with that described in this article but the site of the ductus arteriosus was not identified at operation for congenital cardiac disease. Since the aortic configuration in these cases was the same as it is in Group II-C-1, except for minor difference in the origin of the subclavian arteries, it is reasonable to postulate that the ductus arteriosus was situated on the right side.

D Right-Sided Aortic Arch and Upper Portion of the Descending Aorta on the Right Side —1 Left Subclavian Artery Originating from the Aortic Arch or from the Descending Aorta—If one studies the double aortic arch of Group II (fig. 132a) and assumes that that portion of the left arch between the origin of the left common carotid artery and that of the left subclavian artery disappears he will have a clear understanding of the anomaly illustrated in figure 133c. It is characterized by the presence of only one arch, that is the right. This passes over the right major bronchus and blends with the descending aorta the upper portion of which lies in the right side of the thorax. The branches of the aorta from before backward are the left common carotid the right common carotid the right subclavian and the left subclavian arteries.^{1 2 3 4} Figures 132a and 133c illustrate that the very first part of the left subclavian artery is actually the remaining posterior extremity

of a left aortic arch. The configuration of this anomaly is essentially a mirror image of that illustrated in figure 131c, that is, it is a mirror image of the common anomaly in which the right subclavian artery arises as a fourth branch of an otherwise normal aorta. As is true in cases of that configuration, the aorta does not interfere with either the esophagus or the trachea but the subclavian artery, which crosses the midline, usually behind the esophagus, may compress that tube and cause dysphagia.

2 *Right-Sided Aortic Arch and Upper Portion of the Descending Aorta on the Right Side. Left Subclavian Artery Originating from Left-Sided Innominate Artery*—This is the most common type of anomaly in Group II. The pattern of the aortic arch and of its branches is a mirror image of that of the normal aorta. The aortic arch passes over the right major bronchus and blends with the descending aorta, the upper portion of which lies to the right of the esophagus and to the right of the midline. In the lower part of the thorax the descending aorta crosses to the left and enters the abdomen through the aortic hiatus of the diaphragm. Figures 132a and 133d reveal that this anomaly is a modification of the double aortic arch of Group II in the following respects. That portion of the left arch posterior to the origin of the subclavian artery disappears, the left subclavian artery arises, therefore, in common with the left common carotid artery from a left-sided innominate artery. The left-sided innominate artery is the first branch of the aortic arch, the right common carotid and right subclavian arteries are the second and third branches, respectively.^{16 39 44} Since the aortic arch, its branches, and the upper part of the descending aorta are mirror images of the structures of the normal aorta, they do not encroach upon the trachea or the esophagus and symptoms relative to interference with the function of either of these tubes by the vascular anomaly are not ordinarily encountered. It is of interest that the anomaly being considered is frequently associated with congenital cardiac disease, particularly with the tetralogy of Fallot. According to Taussig, about 20 to 25 per cent of patients with the tetralogy of Fallot have this aortic configuration.⁴⁶ The other types of malformations de-

rived from the aortic arch derivatives may be associated with congenital cardiac disease but that is not the rule

TREATMENT

If a patient suffers from symptoms resulting from an anomaly of the derivatives of the aortic arch system certain rules concerning surgical therapy can usually be followed. Relief may be obtained by division of the smaller of the two aortic arches, by division of that part of the arch which is atretic, by division of the ductus arteriosus, by dislocation of a common carotid artery, or by division of a subclavian artery. Usually, the structure or structures which must be treated surgically are either the ductus arteriosus or some structure which lies in the same side of the body as the ductus, therefore, it is advantageous for the surgeon to know, pre-operatively, on which side the ductus arteriosus lies in order that he may perform the thoracotomy on that side. Since the roentgenologist is not able to visualize the ductus arteriosus directly he must rely on indirect evidence in predicting its situation. The following rule, although not infallible will be helpful. The ductus arteriosus usually lies on the same side of the thorax as does the upper portion of the descending aorta. By visualizing the site of the latter structure, the roentgenologist may predict, with reasonable accuracy, the situation of the ductus arteriosus and guide the surgeon as to the proper side on which to perform the thoracotomy.

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CLINICS ON OTHER SUBJECTS

SOME RECENT ADVANCES IN STUDY OF THE THYROID THEIR INFLUENCE ON THE TREATMENT OF THYROID DISEASES

SAMUEL F HAINES, MAVIS P KELSEY, MARVIN M D WILLIAMS,
AND F RAYMOND KEATING, JR

IN recent years, several new tools have become available for study of the thyroid gland. These include methods, however inaccurate, for the determination of thyrotropic hormone, goitrogenic drugs, including thiouracil and related substances and radioiodine. The recent advances which these new tools have made possible, both in the study of thyroid function and in the treatment of thyroid diseases, have overshadowed any advances made in this particular field for many years. Since 1923, when H S Plummer established the value of iodine in the treatment of exophthalmic goiter, much work has been done in attempts to determine (1) the reasons for the effectiveness of iodine in this disease, (2) the reason for the lack of effectiveness of iodine in adenomatous goiter with hyperthyroidism, and (3) the methods by which the thyroid gland, either normal or abnormal, handles iodine when it is present in either normal or abnormal amounts. Studies of the content of iodine in blood and tissues led to a somewhat better understanding of thyroid function, but methods for determination of the iodine content of the blood were not easy to follow, and variations in the methods led to results which were considerably at variance. Because of the technical difficulties of the methods, determinations of the iodine content of the blood never has been widely employed clinically, except in a few medical centers in which thyroid disease is extensively seen and treated.

THYROTROPIC HORMONE

Studies of the thyrotropic hormone also have occupied an important place in the thyroid investigations of recent years. The methods for determination of thyrotropic hormone have

been too laborious and the results too uncertain to make this determination widely favored. However, in those institutions in which this substance has been studied, considerable advances in the knowledge of thyroid disease have resulted. The relationship of the thyrotropic hormone to exophthalmos has been the subject of much study. Experimental evidence indicates that there is a direct relationship between the presence of thyrotropic hormone in excess and exophthalmos in some laboratory animals, and an inverse relationship between the amount of thyroid tissue present in the animal and the degree of exophthalmos. Attempts to correlate the experimental and clinical observations never have been too conclusive, largely because of uncertainty in the determination of the thyrotropic hormone. Rawson's demonstration of inactivation of thyrotropic hormone by thyroid tissue³² constitutes a considerable advance in the study of this substance, but much remains to be done before any sound knowledge emerges regarding the possible relationship between thyrotropic hormone and various thyroid diseases in human beings. Results of clinical and experimental studies by Soley, Dobyns⁹ and others established the fact that protrusion of the ocular globes usually increased after removal of the normal thyroid glands in animals or after resection of the diseased thyroid glands in human beings. Subsequently, these studies were extended to demonstrate a protrusion of the ocular globes after control of hyperthyroidism in human beings by other means than surgical resection, and a recession of the position of the globes after the treatment of myxedema in human beings.¹¹ Interpretation of the latter finding is somewhat confused by the changes in fluid balance which result from the treatment of myxedema, and the exact clinical significance of these studies is not clear. Edema and an increase in the size of the orbital muscles were demonstrated by Naffziger, Brain and others in the severe exophthalmos of Graves's disease. Later, Rundle and Pochin, in chemical studies, found that an increase in orbital fat occurs in patients who have Graves's disease, with or without severe exophthalmos. Dobyns confirmed the latter finding by microscopic studies. In experimental animals he also has demonstrated¹⁰ that an increase in

the fat content of other than orbital muscles follows the administration of thyrotropic hormone and he has, moreover, demonstrated in these animals a generalized disturbance in deposits of fat in the body, a disturbance which is characterized chiefly by phagocytosis of fat and by edema. The observations of Paulson on guinea pigs and of Albert on killifish (*Fundulus*) indicate that an excess of fluid occurs in the orbital tissues of animals treated with thyrotropic hormone. These observations may have some clinical correlation with the frequent fluctuating swelling of the lids seen in patients with the exophthalmos of Graves's disease, but this correlation is not clearly established. Rundle and Pochin have assigned more importance to fat as a cause of the swollen lids in this condition. The ease and rapidity with which the swelling changes make it likely, however, that fluids are important constituents of the swollen tissues, and the results of Dobyns' studies of various tissues of animals treated with thyrotropic hormone lend some support to this contention.

GOITROGENIC DRUGS

In 1943 Astwood announced the results of his important studies on the effects of thiourea and thiouracil in Graves's disease. Many years before, Chesney, Clawson and Webster had noted the goitrogenic effect of a cabbage diet in rabbits; subsequently, Marine and others determined that this effect was caused by the nitrile content of this diet. The Mackenzies then had shown that in animals a similar effect occurs in association with some of the sulfonamides, chiefly sulfaguanidine.²⁶ It remained for Astwood to extend these studies and to apply the knowledge thus gained to the treatment of Graves's disease.

Using radioiodine collections as a measure, Larson and one of us (Keating) and associates^{27,28} found that thiouracil prevented all but small amounts of iodine from being collected by the thyroid glands. Thyrotropic hormone, on the other hand, caused a loss of iodine already present in the thyroid glands and increased the demand of the gland for iodine. Paschalis and his associates found that thiouracil prevented the elaboration of thyroxin in the thyroid glands by inhibiting

certain enzyme activity Rawson and his associates³⁴ found that under treatment with thiouracil the hyperplastic thyroid gland in Graves's disease became more hyperplastic and that thiouracil prevented the proper utilization of iodine by the thyroid glands, but that, in spite of the latter effect, iodine produced involution of the thyroid glands. They, therefore, postulated that iodine has two effects in the thyroid glands that of iodinating the thyroprotein and that of producing involution, and they suggested that the two actions were separate. Albert and his associates added an important study in which they determined that thiouracil increased the effectiveness of thyrotropic hormones, and that iodine inactivated thyrotropic hormones, causing a precipitate that later could be dissolved and reactivated by thiouracil.

In summary, then, thiouracil was found to prevent the elaboration of thyroxin in the thyroid glands and also to cause the development of hypertrophy of the thyroid cells. Potassium thiocyanate had a different effect, probably due to the fact that it prevented the thyroid glands from collecting iodine, also, this effect was much less constantly obtained in human beings than was the effect of thiouracil. The effect of cyanates was abolished by the simultaneous administration of iodine, but that of thiouracil and related drugs was not. Thiouracil administered in sufficient doses over a considerable period was found to produce enlargement of the thyroid glands, hypertrophy of the cells, and the clinical picture of myxedema. The same also was true of potassium thiocyanate, but in the case of the latter drug this effect occurred very rarely. Rawson's case,³³ reported late in 1943, was the most striking example of potassium thiocyanate goiter which has yet been published, and the most carefully studied. Biopsy of a specimen of the thyroid glands taken while the patient had myxedema showed extreme hypertrophy of the thyroid epithelium.

It is apparent that as yet there is not complete understanding of the function of the thyroid glands, either normal or diseased, but thiouracil has been and continues to be an effective tool in the study of thyroid function, and it has added much to knowledge of these glands.

Soon after Astwood announced his discovery of the control of hyperthyroidism by thiouracil in cases of Graves's disease, the drug became available to many investigators for use in treatment. Its effect in the control of hyperthyroidism was startling, and the effect was obtained with great constancy. Soon, however, various untoward reactions to the drug began to appear, and in a very short time it had become apparent that agranulocytosis occurred after the use of thiouracil in a small but significant number of cases. Because of this danger, it was essential that all patients taking the drug remain under close medical observation, and even under those circumstances fatal agranulocytosis was known to occur. Some observers, notably Bartels and his associates²² at the Lahey Clinic, Means and his associates at the Massachusetts General Hospital, our own group, and others, used the drug chiefly in pre-operative treatment. Its success in this respect was striking. Patients with unusually severe hyperthyroidism and those with serious complicating diseases which were aggravated by hyperthyroidism were, after preparation with thiouracil, so greatly improved that their operations were done with minimal risk. Because of excessive bleeding from the thyroid glands of patients prepared for surgical treatment only with thiouracil, iodine was added during part or all of the time that thiouracil was administered, and it was soon found that the hyperplasia and loss of colloid produced by thiouracil could be made to involute by iodine, and that the excessive bleeding was thus avoided. Astwood and Vander Laan, meanwhile, continued their study of hundreds of goitrogenic drugs, chiefly those related to thiouracil, and carried out clinical trials of the most promising ones. Diethyl thiobarbituric acid (thiobarbital) was one such drug which offered great promise, but it, like others, produced too many untoward reactions to be widely accepted. When propylthiouracil was introduced, the treatment of Graves's disease by goitrogenic drugs received greater impetus, because reactions of a serious nature rarely followed its use. Still it was potentially a toxic drug, and at least one instance of agranulocytosis can be charged to it, so that prolonged administration or use of it without constant observation, seemed of questionable advisability.

Moreover, Williams^{38, 39} of Boston soon showed that of patients treated for Graves's disease solely with thiouracil or related drugs, more than half experienced recurrence of the disease when, after six to twelve months, administration of the drug was discontinued. Propylthiouracil became the drug of choice in the preoperative preparation of patients with exophthalmic goiter, iodine being administered of course, before surgical treatment was instituted or during the entire time of administration of propylthiouracil. Several investigators continue to use propylthiouracil as the total treatment of Graves's disease, however, and, because of the varied programs which now are being followed, it seems likely that a few years more will allow adequate evaluation of the different programs so that the best one can be determined. The high incidence of recurrence of the disease after treatment with goitrogens, the difficulty in keeping our patients under prolonged observation, and the occurrence of occasional untoward reactions, even from propylthiouracil, have made us hesitate to use the drug as the total treatment for hyperthyroidism except in occasional, unusual instances. As preparation for thyroidectomy, propylthiouracil combined with iodine has been extremely successful. The time needed for effective administration of this drug is considerably greater than the time needed for ordinarily adequate, but less complete preparation with Lugol's solution. Therefore, except when the patient's condition is severe or complicated, we have continued to use Lugol's solution as the preoperative preparation of choice in Graves's disease, because it has been amply demonstrated that for patients who have mild or moderately severe forms of the disease thyroidectomy can be performed after the use of iodine with no greater surgical risk than that inherent in thyroidectomy itself.

RADIOIODINE

In 1934, Fermi first prepared a radioactive isotope of iodine. Subsequently, several others have been prepared. It was apparent from the start that these substances would soon be of great value in the study of thyroid function, but they were not readily available for such investigations, and the

short half-life of those substances first prepared limited studies with them to investigators who worked near a cyclotron. In 1938 Hertz, Roberts and Evans, working in Boston, and Hamilton,¹⁴ working in California, began studies with radioiodine prepared in the cyclotrons which were located, respectively, in Cambridge and in Berkeley. It soon was found that these substances were to occupy an important field in thyroid investigations.

Radiiodine behaves chemically just as stable iodine does, but by means of the radiations given off, its approximate location in the body can be determined. The earlier work was done with short-lived isotopes, of which I^{130} , with a half-life of 12.6 hours, was used most extensively. Subsequently, the preparation of I^{131} in the chain reacting uranium pile has made this isotope, with a half-life of eight days, available to many more investigators and I^{131} now is the most extensively used of the isotopes of iodine. For study of the thyroid glands the important characteristic of I^{131} is that it emits rays which can be detected by the Geiger-Müller counter. Two rays are emitted: (1) beta rays, which are negative electrons and travel only a few millimeters in tissue, but which produce considerable ionization in the tissues through which they pass and (2) gamma rays, which travel long distances with the speed of light, but which produce comparatively little ionization in the tissues through which they pass. Beta rays can be counted only if the substance containing them is in close approximation to the Geiger-Müller counting tube, and such counts therefore, are limited to substances such as urine, blood, properly prepared tissues and the like, which can be placed directly under the counting tube. Gamma rays, because of the distance they travel, can be detected by counting tubes at some distance from the material containing them, and thus the amount of radiiodine in the thyroid glands of living subjects, for example, can be determined by counting of the gamma rays which are given off from those organs. Improvements in counting tubes, in the scaling circuits which record the counts, and in techniques for this type of counting are constantly being made. The technical details of counting and the need for knowledge of radioactive disintegrations are such

that trained physicists are essential parts of any team undertaking studies which involve the use of radioiodine. Furthermore, the presence of radioactivity poses another and a very important problem to the investigator. The use of these substances may be dangerous to those using them or to those receiving them. Precautions must be used in the handling of radioactive substances, and the precautions necessary are such that they impose certain restrictions on methods of handling, on choice of patients to receive them and particularly on the quantities to be administered. Exercise of such precautions requires special apparatus for such purposes as handling of the substances, monitoring of areas used in handling the substances, and disposal of excreta containing appreciable amounts of radioactive isotopes. Personnel repeatedly exposed to radioactivity must be properly protected by lead shields and hoods for the removal of contamination from the air. Constant monitoring both of the area in which they work and of themselves, by the wearing of film badges, must be done to determine exposure. They also should be examined frequently to detect any changes in the skin or in blood cells. Thus, it is apparent that any team using radioiodine in its investigations should include, at the least, a physicist, chemist and hematologist.

Hamilton,¹⁵ as Hertz had done previously, found that the normal thyroid glands had concentrated appreciable amounts of a dose of radioiodine. This amount was found to be variable, but it was about 20 per cent of the administered dose. Patients with exophthalmic goiter had thyroid glands which collected much larger amounts of radioiodine, many of them concentrating 80 per cent of the dose within them. Patients with myxedema, as might be expected, excreted most of the radioiodine and their thyroid glands collected little or none. This was not true, however, of hypothyroid children who had goiter. Hamilton, Soley, Reilly and Eichorn found that these atrophic thyroid glands, presumably hypertrophied glands, collected considerable amounts of iodine. Later, it was found that thyroid glands made hypertrophic by the administration of potassium thiocyanate or thiouracil had an increased ability to collect iodine after the drug had been excreted. Hamilton

and his associates,¹⁷ Gross and Leblond, and Cope and others have used the autoradiograph to demonstrate the collection of iodine by the thyroid glands and to indicate varying amounts of iodine collected by adenomas and extra-adenomatous tissue.

As a direct result of the studies of thyroid function with radioiodine the diagnostic value of this substance has become apparent. Among patients not recently treated with iodine, or thiouracil, or potassium thiocyanate or other goitrogenic drugs, the amount of radioiodine collected by the normal thyroid glands rarely has exceeded 30 per cent, and the amount collected by the thyroid glands of a hyperthyroid person rarely has been as low as 30 per cent. If the radioiodine excreted in the urine is determined at frequent intervals, it is apparent that in patients with exophthalmic goiter the rate of excretion is rapid but the total quantity excreted is small. This fact led to the statistical analysis of urinary excretion curves by Berkson, Power and two of us (Keating and Haines).¹ Recently, we have described the careful analysis of many such curves. It cannot be said at present that the urinary excretion curves are absolutely pathognomonic, for, rarely we have seen essentially normal excretion curves in patients who had proved exophthalmic goiter. However, in general, the form of the curve of excretion of radioiodine and the total amount of radioiodine excreted give valuable information about the pathologic status of the thyroid glands.

Soon after the initiation of its use in thyroid investigation, radioiodine began to be considered as a possible therapeutic agent in thyroid diseases. This work, too, was limited at first to those centers which were located near cyclotrons. Hamilton and Lawrence used radioiodine in the treatment of Graves's disease, but the first comprehensive reports in the literature were those of Hertz and Roberts, and of Chapman and Evans in 1946. The radioiodine isotope used in their studies was a mixture comprising 90 per cent I^{130} (with a half-life of 12.6 hours) and about 10 per cent I^{131} (with a half-life of eight days). Although most of the effect was attributed by these authors to I^{130} , the total effect of I^{131} may have been considerable. These investigators treated patients with exophthalmic goiter by oral administration of the

isotopes As was to be expected, large amounts of the administered radioiodine were collected by the thyroid glands, and in varying periods of time the symptoms and signs of hyperthyroidism were reduced Repeated doses were needed in some cases to bring the basal metabolic rates to normal and to hold them there It is apparent from these reports that radioiodine is an effective therapeutic agent Biopsy of a specimen taken from the previously treated thyroid glands of a patient who had Graves's disease showed marked fibrosis of the gland and deterioration of the remaining follicles It is noteworthy, however, that those epithelial cells which remained were of the high columnal type characteristic of Graves's disease

In 1946 the Clinton Laboratories at Oak Ridge, Tennessee, began distributing radioiodine (I^{131}) for use in study of the thyroid glands Since that time much more work has been done on the therapeutic application of this material Dosage was uncertain at first, and the knowledge gained by studies with I^{130} could not be applied directly to I^{131} Our studies along this line have been carried out slowly, because we are hesitant to supplant proved methods of treatment with a method which is still experimental Questions have been raised as to the possible carcinogenic effect of radiation administered in this manner, and it has not yet been demonstrated conclusively that ill effects will not be produced on other organs than the thyroid glands Therefore, we have chosen as subjects for treatment with radioiodine patients with hyperthyroidism, and particularly Graves's disease, for whom other forms of treatment would be especially hazardous Such selection includes those patients with serious heart disease and exophthalmic goiter, some who have experienced multiple recurrences after surgical treatment, and some in whom large recurrent goiters on one side were complicated by paralyzed vocal cords on the opposite side Regardless of complications, we have not yet felt justified in using radioiodine in the treatment of Graves's disease in young people

Our procedure in treatment is similar to that customarily used When it is decided that the patient is to receive this form of treatment, the tracer dose of 100 microcuries of I^{131} ,

with 100 micrograms of sodium iodide to act as carrier, has been given orally. The amount of iodine excreted in the urine in seventy-two hours is, as previously noted, a fairly good criterion of the approximate collection by the thyroid glands. The weight of thyroid tissue is estimated. This estimate is inaccurate, but with considerable practice it can be reasonably close. The dose to be administered is then calculated. We generally have employed a dose which would allow the thyroid glands to collect about 200 to 250 microcuries of radioiodine per estimated gram of tissue.

Within a few days of the administration of such a dose, the thyroid glands usually become harder and may be slightly tender. A reaction has occurred in only one of our cases, and it is uncertain as to whether that represented (1) a hyperthyroid reaction caused by rapid destruction of a part of the glands and subsequent liberation of its contents or (2) "radiation sickness." The patient had slight fever and malaise for three or four days.

Beneficial results are noted at variable times. In some instances, relief of symptoms of hyperthyroidism has occurred within a few weeks, but in others improvement has been slow and gradual for a few months. Reduction in the size of the glands is to be expected, but it is slow in occurring. Most of the patients we have treated have been completely relieved of all evidences of hyperthyroidism. In a few instances, multiple doses have been needed. Recurrences necessitating more treatment have been noted a few times, and in some cases myxedema has followed the treatment. It is far too early in the course of our investigations to permit evaluation of this method of treatment, but it seems reasonable to assume that hyperthyroidism can be ameliorated or controlled with adequate doses of radioiodine. Whether or not untoward reactions may occur can be determined only after several years. Most of the patients we have treated with radioiodine have sharply limited life expectancies because of the coexistence of other diseases.

In view of the large amounts of radiation which can be introduced into tissues by the administration of radioiodine—much larger amounts than can be given by radium or roentgen

rays applied externally—the possibility of treatment of cancer of the thyroid glands has received considerable attention. Leider, Seidlin, Marinelli and Baumann, and Seidlin, Marinelli and Oshry have reported the control of metastatic lesions from cancer of the thyroid glands by means of radioiodine. Unfortunately, the greater number of cancers of the thyroid glands do not show much tendency to collect iodine. This has been demonstrated by Marinelli, Foote and Hocker who used autoradiographs. Various means have been employed in attempts to increase the collection of iodine by malignant tissue, and among others, it has been found that the production of myxedema either by surgical extirpation of the entire thyroid gland or by the administration of a large dose of radioiodine may in some instances result in an increased collection of iodine by the metastatic lesions of cancer of the thyroid gland. It is far too early in our experience to allow us to say whether or not malignant tissue which will collect radioiodine can be destroyed by I^{131} . Judging from the experiences of the aforementioned investigators, it is well worth trying but, as in other instances, we have hesitated to supplant a proved and effective method of treatment with an untried one, so that we have limited our efforts in this regard to patients whose lesions are proved to be inoperable.

Whether our hopes for radioiodine in the treatment of cancer of the thyroid glands will materialize can be determined only after several years of study. Whether it will continue to be used as a therapeutic measure in hyperthyroidism will be determined largely by whether or not secondary and undesirable effects develop. Barring the development of such effects, radioiodine will be a very useful form of treatment, in at least some cases of thyrotoxicosis, and it will be a diagnostic aid of considerable value. It also is clear that propylthiouracil or some related drug will continue to be useful in the preoperative treatment, if not as the total treatment, in some cases of thyrotoxicosis. Regardless of their place in the ultimate therapeutic armamentarium directed against thyrotoxicosis, both substances have been and will continue to be of inestimable value in the study of the physiology and pathologic physiology of the thyroid glands. Im-

provements in methods for determination of the thyrotropic hormone also should add materially to knowledge of the pathologic processes that occur in the thyroid glands, as will determinations of inorganic and of protein-bound iodine in blood and tissues. The value of these investigations will be considerably enhanced by studies of the dynamics of iodine metabolism which can now be carried out with radioiodine. Simultaneous studies of all these factors in the same patient, and extension of them to the various diseased thyroid states, would seem, at present, to offer productive lines of investigation. Advances in medical knowledge usually are made slowly and by hard work, the last ten years have seen more rapid advances in the knowledge of the physiology and disease of the thyroid glands than anyone could have anticipated. But there still is a long way to go before we have anything like complete information about the thyroid glands and all aspects of their function. Fortunately, those studies which have added materially to knowledge of thyroid function in health and disease have also added materially to the effectiveness and safety of the treatment of patients with thyroid diseases.

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THE PRESENT-DAY THERAPY OF THROMBO- ULCERATIVE (STREPTOCOCCAL) COLITIS

J. ARNOLD BARGEN

In this article that form of ulcerative colitis which has its inception in the most distal portion of the rectum and spreads relentlessly orad from that point will be considered. The wall of the bowel is involved primarily and diffusely and the mucous membrane only secondarily. The lesion begins in the submucosal structures as a thrombotic process. The mucous membrane becomes granular and edematous and bleeds easily, and diffuse narrowing of the lumen and general thickening of the wall of the intestine develop. Such a pathologic process naturally is associated with well-defined symptoms, which vary with the progression of the disease and the interjection of various complications and sequelae. This condition has been commonly designated as "thrombo-ulcerative colitis," "chronic ulcerative colitis" or "streptococcal ulcerative colitis."

TREATMENT

In thrombo-ulcerative colitis wise guidance of the patient by the general practitioner for a long period and close co-operation of the internist and surgeon are essential. Treatment should rest on the convictions (1) that the condition is an infectious disease of the large intestine, (2) that uncomplicated cases constitute a medical problem and (3) that certain complications are definite indications for operation. The attitude of physicians toward the disease has changed in the last decade from one of hopelessness and despair to one of hopeful accomplishment. It is well, however, to speak not of cure but of control of this disease.

Medical Management — Thrombo-ulcerative colitis which is not complicated by neoplasm, polyposis, stricture, perirectal abscess, perforation or nephrolithiasis is in general a medical problem. Patience and perseverance on the part of the physician and an optimistic viewpoint from the patient are essential in the treatment of this disease. It is often necessary to start the treatment of patients in the hospital, where

their activities can be controlled accurately, even though they may not be acutely ill

Rest and Restful Recreation—For acute, fulminating thrombo-ulcerative colitis, rest in bed and absolute quiet should be maintained until fever has disappeared. Then physical activity should be resumed gradually. To rest the intestinal tract it may be necessary to withhold food by mouth and to give fluids parenterally. For the patient who has a more chronic, although severe condition, without fever, restful recreation is important. The patient should not be kept in bed but should follow a positive program of mild activity. Reading, short walks and mental diversion are helpful. Easy discouragement seems to be a feature of the disease. The slightest change of symptoms which is not for the better may undo days of improvement because of the patient's mental attitude toward such a change. Occupational therapy in many forms can be made interesting. This type of diversion is invaluable, for it tends to distract the attention of the patient from his need of remaining near a toilet.

Diet—Feeding of the patients presents one of the most difficult dietary problems in medicine. In the past the amount of food allowed these patients often has been restricted too much, and as a result their strength and ability to fight the infection have been lost. In the active stage of the disease appetite lags or fails. The problem, then, is first one of creating an appetite, and next, of giving foods which are digested almost entirely in the stomach and small intestine, and which thus leave little residue for the colon. The foods prescribed should vary with the stage, severity and complications of the disease. When the symptoms are acute, the patient may be able to take only a small amount of highly concentrated food. In the more severe cases, it may be necessary for a time to give nothing but liquids by mouth. In the worst cases intravenous injection of a solution of glucose and subcutaneous injection of large amounts of physiologic solution of sodium chloride can be employed.

In the average case the food given should not be irritating, should have a low residue and an adequate content of calories, proteins, vitamins and minerals, and should be as attractive

as possible. Some of the foods which have a low residue are lean meats, rice, white bread, Italian pastes, sugar, well-cooked and strained cereals, cooked eggs, butter and cream. Proteins in most forms are very desirable. Vitamins can be supplied in concentrated form in fruit juices, yeast, butter, wheat germ, cod liver oil extract or irradiated ergosterol. Milk is not a low-residue food, and it is not well tolerated by many patients. Boiling the milk makes it slightly more digestible.

On admission to hospital, or when treatment is begun, the patient is given strictly bland food, to which additions are made at regular intervals. The foundation diet or the foundation diet with additions may be given, but few patients will tolerate the full diet from the beginning.

Additions to the foundation diet will result in a full diet which provides for 140 gm. of protein and 3,400 calories a day. Jelly or jams without seeds may be served if desired. Iced beverages should not be given. Ice cream should be eaten very slowly. Condiments, such as mustard, horseradish, catchup, vinegar and highly seasoned sauces or relishes, are best avoided.

The diet based on these broad, general principles, should be adjusted to the needs of each patient. Few patients react similarly to any given program.

Vitamins—Occasionally, in the late stages of thrombo-ulcerative colitis, peripheral neuritis has been noted which responded dramatically to large doses of thiamine chloride. On a few occasions too marked reduction of dark adaptation has been encountered. This condition improved when large amounts at times as much as 100,000 international units, of vitamin A were given daily. In more cases the ascorbic acid content of the blood serum has been found to be low because the patients have been afraid to take adequate quantities of citrus fruits. Such patients have been aided materially by being given 200 to 300 mg. of synthetic vitamin C in tablet form daily. In a rare case several massive hemorrhages may occur because of a reduction of the concentration of prothrombin in the blood. Administration of vitamin K, klotogen (a concentrate containing vitamin K in peanut oil)

6 to 9 capsules by mouth or menadione (2-methyl-1, 4-naphthoquinone) 1 grain (0.065 gm) by vein has given prompt relief

Except for these exceptional situations vitamin concentrates are furnished to these patients only in a supportive manner. The diet, however, should be planned so that no essential food or vitamin will be lacking. The syrups or elixirs of vitamin B complex have been found helpful in stimulating the appetite and from that standpoint seem worthwhile. At the stage in the progress of recuperation from this disease at which large amounts of vitamin concentrates can be given by mouth, the patient should be able to eat well and generously.

Vaccine — When improvement comes, and in milder and earlier cases, a bacterin, prepared as an autogenous vaccine from the organism found in the rectal ulcers in each case, is administered subcutaneously every three to five days for several months. The dose which is 0.1 cc. at first is increased at each injection by 0.1 cc., until an average maximum of 1.5 cc. is reached. After a rest of several months, the same procedure is repeated. Three or four such courses are administered, or the vaccine is given until the patient is free of symptoms. After that an occasional course of vaccine is given for several years.

Nursing Care — Since rest in bed usually is prescribed for the initial part of the treatment, and often for weeks during an acute exacerbation, the systematic execution of the many details necessary for comfort and peace of mind, as well as for actual physical progress of the patient, can be accomplished only by careful nursing. This may be by the hospital staff or by helpful persons in the home. Freedom from worry and emotional strain is important for the patient. Fatigue and nervous excitability interfere with a patient's progress. It is important to keep the patient warm and to maintain the body fluids. Occasionally hot abdominal stupes seem to give much comfort. The great urgency to defecate, which seizes these patients and the straining at the stool, to which they are so prone, must be allayed. This can be done by judicious psychotherapy. Sufficient sleep is most helpful. The many

little comforts which are accorded patients who have any serious illness cannot be overemphasized in these cases

Drugs and Antibiotics—Among the sulfonamide drugs which to date have been found to be useful because of their relative lack of toxicity and therapeutic effectiveness for thrombo ulcerative colitis are azosulfamide (neoprontosil) and certain compounds of sulfathiazole. It has been found that most of these drugs are best given in courses of two weeks followed by a rest period of a week and then another course is given for a similar period. In this way 60 to 90 grains (4 to 6 gm.) of azosulfamide (neoprontosil) can be given each twenty-four hours in divided doses to the average adult. For children the dose will be correspondingly smaller. Phthalylsulfathiazole (sulfathalidine) may be given in doses of from 120 to 240 grains (8 to 16 gm.) in twenty-four hours. Although the toxicity of both of these drugs is slight, toxic reactions have been known to occur even with these sulfonamides. When azosulfamide is used, it is particularly important to determine the concentration of hemoglobin and the number of erythrocytes and leukocytes frequently, since anemia is likely to occur while the drug is being administered. Sulfathiazole in doses of 45 to 75 grains (3 to 5 gm.) daily is well tolerated but careful watch must be kept for toxic effects.

Because of some similarities between acute thrombo-ulcerative colitis and rheumatic fever, the salicylates have been given therapeutic trial in cases of thrombo-ulcerative colitis. Various investigators have tried to prepare combinations of sulfonamide and salicylate drugs and to this end salazopyrin has been prepared and is now distributed commercially in Sweden. Our experiences with this drug have been rather gratifying. From 75 to 120 grains (5 to 8 gm.) a day can be given in divided doses in the same way that the other sulfonamides are administered.

In cases of acute fulminating ulcerative colitis some of the other drugs such as sulfadiazine are indicated. They should be administered in suitable concentrates so that at least 12 to 15 mg. of the drug is found per 100 cc. in the blood. A striking effect has followed the administration of each of these drugs.

in selected cases. Maximal results will be obtained when the drug of choice is used early in the course of the disease.

A chemotherapeutic agent cannot be expected to restore to normal the physiologic function of a bowel which has become contracted and deformed by a disease of long standing. One may hope that the drug will help control symptoms due to active infection.

Several antibiotics have been given a clinical therapeutic trial in the control of the active symptoms of ulcerative colitis. Penicillin is the only one which has proved helpful. Its greatest therapeutic value lies in its administration to the very sick patients who have ulcerative colitis. The intramuscular administration of 50,000 to 60,000 units every three hours to patients who have high fever, are passing many bloody, purulent, rectal stools, are wasting rapidly and have all the concomitants of a severe debilitating illness often has resulted in a dramatic control of symptoms. This antibiotic may be given over a considerable period of time, at least ten days or two weeks. In some cases as much as 100,000 units every three hours is required. More recently various preparations of penicillin, such as those prepared with calcium, have been given by mouth. Other preparations have been put up in suppositories and have been given in this way. So far no important results have been achieved in administering penicillin by any of these methods to severely ill patients who have thrombo-ulcerative colitis. Perhaps a better way of administering this antibiotic to these patients is in the offing.

Results of trial of streptomycin have not been encouraging in the treatment of this disease.

Oxygen —With the advent of the BLB mask and ability to administer oxygen in concentrations up to 100 per cent in an easy manner, efforts were made to control the critical stage of this infection with oxygen. Striking immediate help accrued to a few patients. In these cases oxygen has changed a severe toxic state with high fever, rapid thready pulse and cyanosis to one of comfort, with decrease of temperature and return of normal color to the fingers.

Transfusions —Blood may be given for several reasons (1) to fight the toxemia attendant on sepsis and depletion,

(2) for anemia and the weakness following loss of blood, (3) for hypoproteinemia or (4) for general debility caused by disease of long standing. Two to five transfusions of 150 to 250 cc each have much greater value than has one transfusion, or more than one, of 500 cc or thereabouts. From three to four days should elapse between the transfusions of small amounts.

Irrigations and Instillations—My experience, as well as that of many other clinicians, is that the good which may be accomplished by the so-called disinfecting irrigations is offset by the irritation they cause. It is essential to remember that no matter how powerful a disinfectant is used for the irrigation, the procedure will not eradicate the infection since the disease extends deeply through all the layers of the bowel, and at times into the mesentery and even into the blood stream. Consequently, the most that is accomplished by intestinal irrigation is cleansing of the surface, and that only for a few minutes. In cases in which there is much perianal infection, as there is in cases of fistula, irrigation of the rectum with warm physiologic saline solution has given comfort. In those few cases in which such irrigations seem indicated, physiologic saline solution offers as much as, or more than, solutions of silver nitrate, mild silver protein, acriflavine or any of the many other solutions which have been tried.

When the disease is confined to the rectum and sigmoid the careful instillation of a warm thin cod liver oil, 1 to 3 fluid-ounces (30 to 90 cc.) at bedtime has been of considerable help. Instillations of powders such as bismuth, of witch hazel or of silica gel also seem to have been employed with advantage. When a massive hemorrhage is occurring, instillation of 3 to 4 ounces (90 to 120 gm) of starch, mixed with warm water and made into a thick paste so that it just flows, into the rectum, has been known to stop such a hemorrhage. The addition of 1 grain (0.065 gm) of powdered opium to this material has proved of advantage.

Removal of Foci of Infection—Since foci of infection may serve as depots from which infection of the bowel may arise, accessible ones should be removed if possible. Teeth that have periapical abscesses and suspicious looking or definitely infected tonsils should be removed. The tender and inflamed

rectal wall usually will prevent the massage necessary to clear up prostatitis. Perineal infections, cryptitis and papillitis should be treated cautiously. In general foci of infection should be removed while the disease is in the stage of remission, or at least of quiescence.

Parenteral Administration of Fluids—Parenteral administration of fluids is often necessary. The solutions used are (1) physiologic solution of sodium chloride, 9.0 gm of sodium chloride per liter, (2) a modified Ringer's solution consisting of 9.0 gm of sodium chloride, 0.24 gm of calcium chloride, 0.42 gm of potassium chloride, 0.20 gm of sodium bicarbonate and 1,000 cc of triple distilled water, (3) duodenal replacement formula (D. R.) made of 7.0 gm of sodium chloride, 0.90 gm of potassium chloride, 0.34 gm of calcium chloride, 0.28 gm of magnesium chloride and 1,000 cc of triple distilled water and (4) modified Hartmann's solution consisting of 4.8 cc of sodium lactate, 12.0 gm of sodium chloride, 0.8 gm of potassium chloride, 0.4 gm of calcium chloride and 2 liters of solution. The main constituent of all of these solutions is sodium chloride in a concentration which is isotonic or slightly hypotonic. The last three solutions contain other ions which are helpful but perhaps of secondary importance. Two other solutions used for parenteral administration are 5 per cent and 10 per cent solutions of glucose in distilled water and 5 and 10 per cent solutions of glucose in physiologic saline solution.

Parenteral administration of fluids is indicated for dehydration, acidosis or alkalosis and in order to maintain the water balance, mineral balance and nutrition.

The patient who has not lost an abnormal quantity of fluid requires from 2 to 3 liters of fluid a day in order to maintain adequate urinary output of 1,200 to 1,500 cc a day and to replace the fluid lost in sweating. As much as 3 liters may be lost by sweating. Hence a larger quantity of fluid should be given when loss by sweating is great, as in hot weather, in presence of high fever and so forth. Patients who have lost an abnormal quantity of fluid from vomiting, intubation, severe diarrhea and so forth should receive the basal require-

an abdominal intestinal stoma. Men of considerable surgical experience postulated that this infectious process reached a stage at which the changes were irreversible and when the patient arrived at that stage an intestinal stoma, or perhaps even colectomy was indicated. In some instances this was probably true, but the time when a disease process has become irreversible is not known.

Certain late sequelae of the disease, however, present definite surgical problems. The principal ones are polyps, neoplasms, strictures, extensive perianal fistulas, localized perforations and abscesses of one kind or another. Except for these and such essential operations as those for acute intercurrent surgical disease, surgical treatment should be used seldom.

The hope has recurred frequently that cure of this disease might be obtained by deflecting the current of intestinal content out of the abdomen. Various methods of doing this were tried. Ileostomy was found to be the procedure of choice. Cattell put the problem of some of the patients suffering from this disease aptly when he said that "ileostomy is the price that some patients must pay for life." He, however, considered the disease primarily a medical problem.

I tried to find out what type of patient thrived best with an ileac stoma, and so carefully analyzed the records of eighteen patients who were known to be living fifteen to twenty-four years after ileostomy. Ten of the patients were women and eight were men. The average age of these patients at the time the ileostomy was made was thirty-two years. The average duration of symptoms of ulcerative colitis prior to ileostomy was four and a half years. Thirteen of the patients had the ileostomy because they had had intractable symptoms without any severe exacerbations. Four of the patients were operated on for an acute exacerbation of their disease and one for a rectal stricture and persistent perirectal infection. Seven of the eighteen patients had colectomy after ileostomy and thus had no further colonic disease. Thus in the majority of these cases the disease had been present for a relatively short period, the patients were young adults and, therefore, more able to adjust their lives to the handicaps

imposed by the ileac stoma than older patients. Operation was performed on most of the patients for chronic intractable symptoms.

It becomes obvious then that when the disease has advanced so far that ileostomy is advisable, colectomy usually should be performed at a later date and as soon as the patient's condition warrants. In most cases it is well to postpone colectomy at least six or eight weeks after the ileostomy.

Medical management should proceed after ileostomy in the same manner as before the operation and if medical treatment is carried out carefully, there will be a few cases in which colectomy will not be necessary and the ileac stoma can be closed reasonably safely.

PROGNOSIS

Thrombo-ulcerative colitis must be considered somewhat as tuberculosis is considered, namely, as a regressive, destructive inflammation of the large intestine in which, to stem the tide many measures must be brought into play, and the patient as well as the physician must suffer long and be patient. Although the present treatment leaves much to be desired, a distinct advance has been made over other previous endeavors.

The life span of patients who have thrombo-ulcerative colitis may be materially abbreviated by the ravages of the disease. This malady can and does relegate a healthy, robust person slowly or relatively quickly to chronic invalidism and intense suffering. By careful continuous management, however, a person so condemned rather often can be restored to normal health and usefulness. It has been found with the passing of time that more and more patients make satisfactory recoveries and are restored to useful citizenship. Once a patient has had this disease, however, he may have to rearrange his mode of living for years to fit with restrictions imposed on him. Just as certain factors predisposing to the disease could be elicited, so also similar factors predisposing to relapse of symptoms are at hand.

Although the results are not so striking in the fulminating group as in others, even here great progress has been made and whereas only a few years ago nearly all of the patients

of this group succumbed to progressive devastating disease, now most of these patients are saved, and interestingly enough, when the patient with the fulminating disease recovers, he usually remains well.

Children of less than twelve years stand the illness poorly and the percentage of recovery when the disease has once caused much damage is relatively small. Although the disease is particularly devastating when it occurs during childhood, this does not preclude the living of a normal span of life by a child so afflicted. From several studies it would appear that when a patient has survived the first years of the disease, the disease tends to become milder, or perhaps, the patient becomes progressively better able to tolerate the condition. Among patients who have passed the age of sixty years when the disease begins, the proportion of recovery is the greatest and approaches 100 per cent. As in most severe chronic infections, however, the onset is commonly in the second and third decades of life. Patients of this age group are usually the sickest, yet they have a high percentage of satisfactory recoveries. Once they have recovered and remain free of relapses, their longevity should not be affected by the fact that they have had the disease.

COMMENT

When the onset is insidious and when it is severe, the tendency is for the first attack to be mild or relatively mild and of short duration, the second to be less mild and of longer duration, and the next more severe and more intractable. Thereafter the remissions between attacks become shorter and shorter until the patient is in continuous trouble. Furthermore, when once an adequate program of management is established remissions become longer and exacerbations progressively less severe and of shorter duration, if they occur at all, until finally the patient remains free of symptoms. This thought must be impressed on the patient so that he or she may not be allowed to become discouraged and will follow an established program without interruption and without trying to take short cuts. This is also true of the patient who has undergone ileostomy.

Whittaker and I analyzed the mental reactions and physical condition of forty patients from months to many years after colectomy had been performed in order to determine the place of the large intestine in the bodily economy. We found that after habits are established, the patients without colons can live just as full and happy lives as those who have colons. No demonstrable physical deficiencies follow colectomy. It does not disturb the physiologic equilibrium of the body generally or of the chemical constituents of the blood, except temporarily. The terminal portion of the ileum becomes demonstrably, although not markedly, dilated after colectomy. A general diet can be taken. Special care of the ileac stoma becomes minimal. Patients are able to resume their economic and social activities. The same advice and precautions about overdoing and prevention of nerve tension, given to the patient whose condition is controlled by medical means, apply to all patients who have had thrombo-ulcerative colitis. Occupations should be such that undue exposure to the elements and great expenditure of nervous energy are not needed and adequate physical and mental rest can be obtained.

If vigilance is maintained after active symptoms have subsided, results may be excellent. Again it may be said that there is analogy between the course of this disease and that of tuberculosis, and every patient who has had a severe attack of ulcerative colitis is always a potential colitis patient. Relapses are common if the medical regimen is not followed assiduously. The most common causes of relapse are (1) infection of the upper part of the respiratory tract, (2) mental and physical trauma and (3) the lighting up of distant foci of infection.

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RECENT ADVANCES IN THE TREATMENT OF MEGACOLON

J ARNOLD BARGEN

PRIMARY megacolon or congenital idiopathic dilatation of the colon is a relatively rare condition. It is commonly defined as a dilatation and hypertrophy of a part of the colon or the whole colon which occurs in the absence of gross obstructive lesions. Although this disease had been described previously, the first classic description was given by Hirschsprung, who defined the disease as "a condition of congenital high grade dilatation of the colon with thickening of all its tunics, especially the tunica muscularis and retention of large quantities of fecal matter."

There is another form of megacolon which causes the same gross anatomic changes as the primary or congenital type and which occurs as the result of slowly progressive and chronic obstruction of the distal segments of the large intestine. This consideration deals primarily with the congenital form of this disease.

Practically every conceivable developmental, anatomic, obstructive, inflammatory and neurogenic defect capable of producing dilatation of the colon has been given by various observers as a cause of primary megacolon¹ (table 1).

Most clinicians do not believe that anatomic variations such as elongation of the sigmoid can account for congenital megacolon. The mesentery is not always elongated in cases of megacolon and there are many persons who have a redundant sigmoid and a long sigmoidal mesentery but do not have megacolon.

Some of the defects listed in table 1 have been encountered only rarely in cases of megacolon. There is no consensus concerning the site of the primary functional obstruction in cases of congenital megacolon but most observers believe that the rectosigmoid is the anatomic site of the dysfunction. Typical congenital megacolon may follow spasm of the sphincter.

Although inflammatory changes may be associated with megacolon, most authors agree that these changes are second-

TABLE 1
CAUSES OF PRIMARY MEGACOLON*

- I Mechanical causes (usually developmental)
 - 1 Extreme mobility of sigmoid (mesosigmoid too long) resulting in torsion
 - 2 Increased length of colon, particularly of sigmoid loop
 - 3 Mucosa of sigmoid thrown into valvelike folds as a result of redundancy
 - 4 Kinking, angulation or adhesions at rectosigmoid
 - 5 Overdevelopment of sphincteric structure at rectosigmoid
 - 6 Spasm of sphincter at the rectosigmoid
 - 7 Aplasia of musculature of rectosigmoid
 - 8 Drag of a sigmoid overload with meconium acting as a valve
 - 9 Partial atresia of anal canal, rectum or sigmoid
 - 10 Imperforate anus (partial)
 - 11 Congenital stricture of the rectum
 - 12 Spasm of anal sphincter due to fissure, ulcer or other cause
- II Inflammatory causes
 - 1 Infective or inflammatory process involving the colon primarily
- III Deranged nervous mechanism
 - 1 Abnormality in sympathetic innervation of longitudinal muscle fibers of colon
 - 2 Neuromuscular segmental defect in colon or paralysis of a segment of intestine
 - 3 Hyperactivity of sympathetic innervation of distal portion of colon (relief by lumbar sympathetic ramisectomy)
 - a Anal achalasia
 - b Achalasia of musculature at rectosigmoid (degenerative changes in Auerbach's plexus)
 - c Disease of sacral autonomic fibers
 - d Vitamin B₁ deficiency as cause of achalasia
 - e Lack of propulsive motility of distal portion of colon

* Modified from Bockus, H. L. *Gastro-enterology* Philadelphia, W. B. Saunders Company, 1946, vol. 2, p. 399

ary to the fecal retention and are not an etiologic factor in the development of primary megacolon

It has recently been shown by Whitehouse, who took his cue from the work of Robertson and Kernohan that the ganglia of the myenteric plexus, particularly of the plexus of Auerbach, are absent in the rectal and rectosigmoidal regions in all cases of primary megacolon. This is undoubtedly an important observation as far as the pathogenesis of primary megacolon is concerned and directly or indirectly forms the basis of the present treatment of this condition

TREATMENT

Under this heading, I shall consider only primary megacolon. Numerous types of medical and surgical treatment have been employed but rapidly have fallen into ill repute

or have been found to be of questionable value I shall consider only those measures that appear to be of value in the treatment of this disease

Medical Treatment —There are two groups of cases in which medical management is indicated and a third, or minor group, in which medical treatment also should be considered

- 1 In cases in which the patients are not more than three or four years of age, medical treatment should be employed as patients of this age tolerate any operation poorly
- 2 In cases in which operation is to be performed, medical treatment should be employed to relieve dehydration, malnutrition and anemia, and to empty the residue which has accumulated in the intestine for years
- 3 In cases in which the disease is mild, medical treatment seems to maintain nutrition and a normal rate of growth Even in these cases, operation occasionally may be required

A large number of drugs have been used in the treatment of congenital megacolon. Acetyl-beta-methylcholine chloride has produced satisfactory results in some cases In some cases, no relapse occurred for three to nine months after administration of the drug was discontinued A case in which death occurred from bromine poisoning as a result of idiosyncrasy to the drug has been reported It has been found that prostigmine bromide augments the action of acetyl-beta-methylcholine chloride, chiefly because it prevents the destruction of acetylcholine, the active principle of the drug by the esterases of the blood

Syntropan (the phosphate of 3-diethylamino-2,2-dimethyl-propylester of tropic acid) a parasympathetic paralyzant which has an action similar to that of atropine in inhibiting the liberation of acetylcholine, has been found of value in certain cases. The physiologic divergence in these different types of drug therapy of congenital megacolon indicates the uncertain ground upon which such therapy rests. An excellent supplementary medical regimen is usually used in conjunction with any reported drug therapy, and the question always arises as to the amount of benefit that might have been derived from this alone

Surgical Treatment —Anal and rectal dilatation originated by Hurst on the basis of his theory of anal achalasia

frequently has been employed in the treatment of megacolon. The use of sympathectomy in the treatment of megacolon first was suggested by Royle and Hunter who noticed that patients with chronic constipation obtained relief when sympathectomy was performed for spastic paralysis. Sympathectomy has been performed relatively frequently for megacolon. Since no single physician sees a very large number of patients with this condition in a lifetime, it is difficult to evaluate the results of this procedure on the basis of personal experience. Since there are many anomalies, for example, macrocolon, which closely resembles megacolon, it is difficult to determine whether or not true megacolon always has been present in reported cases in which good results have been attributed to sympathectomy. Sympathectomy is largely an empirical method of treatment. Learmonth has suggested that it is in the nature of a flanking attack upon the condition.

Various technics have been devised, including particularly presacral neurectomy, that is, the removal of the second to the fourth sympathetic ganglia, inclusive. This operation has some defense in that it infrequently results in sterility in men and loss of function of the vasoconstrictor nerves of the legs which commonly occurs after other forms of sympathectomy have been performed. So far it seems that sympathectomy is best performed on children who are about five or six years of age, provided the severity of the illness does not make it advisable to defer the operation until a later age. It should only be used when conservative treatment has failed. It is not recommended for patients in late childhood and seems to have little value when performed on adults or patients with advanced megacolon.

There are two methods by which one can determine whether or not lumbar sympathectomy will produce a satisfactory result. These are (1) the induction of spinal anesthesia and (2) the administration of acetyl-beta-methylcholine bromide. Either of these procedures should cause active peristalsis and a copious bowel movement if sympathetic inhibition is an etiologic factor in the production of the megacolon.

Sympathectomy is not always indicated in cases in which these tests disclose sympathetic inhibition. The results obtained with sympathectomy seem to vary considerably with

the types of operation employed. In most cases, sympathectomy produces only temporary relief. It is difficult to see how the thick and heavy wall of the involved intestine can change very much after these changes have developed. In cases in which sympathectomy has resulted in a gradual diminution in the size of the colon the patients have been children; the megacolon has not been well developed or the patients probably have had macrocolon instead of megacolon.

Subtotal colectomy seems to be the treatment of choice in cases of advanced megacolon. In cases in which great dilatation and hypertrophy of the colon have occurred no other operative procedure seems to yield satisfactory results. Subtotal colectomy is indicated in three main groups of cases of megacolon.

In cases of segmental megacolon only a small portion of the colon is involved and the adjoining segments are relatively normal. The mortality rate is lower in this type of megacolon than it is in any other type. The technic of subtotal colectomy is simple; the results are exceptionally good and apparently are permanent. There is no tendency for volvulus to develop after operation, as is true in cases in which sympathectomy is performed.

Subtotal colectomy is sometimes indicated in cases in which sympathectomy and subsequent medical treatment have failed to produce satisfactory results.

It might be well to recall here that it also is sometimes indicated in cases in which megacolon is due to mechanical obstruction, and in which medical treatment or surgical removal of the obstruction has failed to produce satisfactory results. I believe that the mortality rate and results of subtotal colectomy in this type of megacolon are about the same as they are in megacolon which is not due to mechanical obstruction.

In addition to these three groups of cases, subtotal colectomy usually should be employed in cases in which spinal anesthesia or the administration of acetylcholine apparently has failed to reduce the size of the involved colon or to reestablish peristaltic activity. In cases in which the patients are males subtotal colectomy should be performed unless sympathectomy is indicated.

In cases in which the patients are infants I do not believe

that subtotal colectomy is justifiable unless there are complications which definitely indicate the use of this procedure

Preoperative Preparation—Patients who have congenital megacolon frequently are dehydrated, malnourished and are suffering from hypovitaminosis, therefore, measures to relieve these complications should be employed before operation is performed. If the physical condition of the patient is good, he should be given a relatively residue-free diet and plenty of hard candy. If the patient's physical condition is poor, a compromise must be made. In this case, a low-residue diet should be employed at first but a relatively residue-free diet should be used for a short time before operation is performed. A saline laxative should be administered once or twice a day. The dose should be based on the age of the patient and on the obstinacy of the constipation. Castor oil, administered in appropriate doses, is the cathartic of choice for emptying the colon in cases in which this proves difficult. The colon should be irrigated twice a day with physiologic salt solution. The content of the colon should be aspirated by way of the rectum the day before operation and as often as necessary on the day of the operation.

It is of the utmost importance to replenish the bodily reserve and nutrition of the patient before operation is performed. The period of replenishment should not be cut short unless such a complication as volvulus or perforation necessitates immediate operation. In such a case, one must make the best of a bad situation. Succinylsulfathiazole or phthalylsulfathiazole should be administered in divided doses. The total daily dose of succinylsulfathiazole should be 240 grains (16 gm) while the total daily dose of phthalylsulfathiazole should be 180 grains (12 gm). Streptomycin may enhance the value of these drugs.

COMPLICATIONS

Volvulus is the most serious complication. It fortunately is rare. The operative mortality for the correction of this condition has been high. In most cases the management may be expectant. Passage of rectal tubes of various sizes has been helpful in some cases. Colonic irrigations administered while

the patient is in the knee-chest position sometimes produce excellent results

A second, much more common complication, which can cause untold discomfort and may require early operation, is fecal impaction. Tremendous masses of feces may be rolled up in the rectum or other portions of the enlarged intestine. I have reported a case in which the fecalith was the size of a large grapefruit and was laminated, which indicated that it had been developing for a long time. The patient had been cognizant of its presence in the upper left quadrant of the abdomen for several years and operation became necessary for its removal.

Peritonitis is another, but very rare, complication. It occasionally is caused by rupture of the bowel. Its treatment again will usually be expectant, and medical, for surgical intervention for this complication is usually fraught with unwarranted risk.

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CLINICAL CONSIDERATIONS OF THE PROBLEM OF EXTRARENAL EXCRETION: PERITONEAL LAVAGE

HOWARD M ODEL, DEWARD O FERRIS, AND MARSCHELLE H
POWER

INTRODUCTION

ACUTE renal failure and uremia occur fairly frequently in patients in whom irreversible renal changes cannot be demonstrated. In this group of patients the mortality rate, unfortunately, is high because of the rapid and marked accumulation in the body of nitrogenous and other waste products which under ordinary circumstances would be excreted by the kidneys.

Many such patients might recover, if a means could be devised to eliminate toxic end products of metabolism during the period of suppressed renal function. Such a means is available in the form of peritoneal lavage. The procedure itself is basically simple, and it should be possible to carry it out with successful results in a high percentage of cases. Yet, in patients in whom its use is indicated, one invariably is dealing with disturbed electrolyte and fluid equilibrium and hence the procedure is fraught with numerous hazards and complications. We believe that many of these hazards and complications can be overcome if certain fundamental principles are understood and carefully observed.

METHODS OF EXTRARENAL EXCRETION

The concept of promoting excretion of nitrogenous and other waste products by extrarenal means in acute renal failure is not new. The older textbooks of medicine advocated induced diaphoresis and purgation as means of eliminating urea and other metabolites from the body in cases of renal insufficiency. In recent years such methods have fallen into disuse because the amount of nitrogen removed from the body through sweating is not great enough to play any significant role in reducing high levels in the blood, and because both methods tend to weaken and dehydrate the patient severely.

The reciprocal or exchange transfusion method, suggested first by Nyiri in 1926, and later by Thalhimer, Solandt and Best after exhaustive studies on nephrectomized animals, was abandoned as undesirable for clinical use after it was shown to require an infinite number of transfusions to lower significantly the nitrogen levels in the blood of the subject, and because of the hazard to both donor and recipient associated with its use

Plasmapheresis, in which procedure uremic blood is drawn, the plasma is separated by centrifugation and the washed erythrocytes are returned to the body suspended in a physiologic solution, likewise has been discarded as a possible means of extrarenal excretion because of serious depletion of plasma proteins resulting in a decrease of the colloidal osmotic pressure of the blood and development of edema

Attempts to substitute for the kidneys, therefore, resolve into two categories those in which the blood is passed through tubes of semipermeable material outside the body, "external" or "extracorporeal dialysis", and those in which a thin natural membrane, such as the mucosa of the gastro-intestinal tract or the peritoneum, is used as the diffusing surface, "internal dialysis"

BASIC PRINCIPLES OF DIALYSIS

All attempts to substitute for the failing kidneys by dialysis are based on several physiologic and physicochemical principles, accurate, detailed and complete elaboration of which is beyond the scope of this discussion. However, in general, the following four statements seem to be applicable

- 1 Crystalloids in solution will diffuse across semipermeable membranes in a way which tends to equalize the concentration of each substance on both sides of the membrane. In other words, if a dialyzing membrane separates two different substances in solution of equal molecular concentration, the substances in these solutions ultimately will diffuse across the membrane so that at the end of dialysis, they will be in equal concentration on both sides of the membrane. If two solutions containing diffusible substances in unequal concentration are separated by a membrane, the diffusible particles will eventually reach identical concentration on both sides of

the membrane, but there will be a temporary shift of water toward the side of higher concentration, proportional in amount to the increased osmotic pressure which the more concentrated solution had originally

2 Colloids such as protein molecules ordinarily will not diffuse across a semipermeable membrane. In general, if such a membrane separates a solution containing a nondiffusible substance on one side and a solution containing a diffusible substance on the other, the concentrations of diffusible non-electrolyte substances per unit of water on each side of the membrane will eventually become equal, but their concentrations per unit of volume will be somewhat less in the solution containing the nondiffusible substance. In addition, the concentrations of electrolyte substances will be further modified, depending on the nature of, and the charge on, the nondiffusible substance (Donnan effect)

3 In the normal kidney, water and crystalloids filter across the wall of the glomerular capillaries to produce a glomerular filtrate similar in all respects to blood plasma except for the absence of protein. Large quantities of water and certain crystalloids needed by the body are selectively reabsorbed by the tubular system

4 Since the action of glomerular filtration is considered to be a purely physical one, it should be possible to substitute a semipermeable membrane for the glomerular filtering surface. There can be no substitute for the selective resorptive function of the tubules, but the necessary water and crystalloids which the tubules ordinarily would conserve can be replaced by parenteral routes

EXTERNAL DIALYSIS

Abel, Rowntree and Turner were the first to devise a method for removing certain substances from the blood by means of external dialysis. Their apparatus consisted of a closed container enclosing a branched system of celloidin tubes through which blood flowed. Dialysis occurred from the blood across the walls of the celloidin tubes into the dialyzing fluid in which the tubes were immersed. As perfusing fluid Abel, Rowntree and Turner used sodium chloride

in 0.6 per cent solution, since they noted the appearance of peripheral edema if sodium chloride in 0.9 per cent solution was used. Successful in the laboratory, their method was not found to be clinically practical owing to the toxicity of the anticoagulant leech extract, hirudin, which was necessary for successful operation of the procedure.

Haas,²⁹⁻³² Necheles,⁵⁰⁻⁵¹ and Thalhimer⁷¹ later constructed external dialyzers utilizing the principles described by Abel, Rowntree and Turner, and employing collodion, tubes of peritoneum, and cellophane as dialyzing membranes.

With the development of heparin as a nontoxic anticoagulant, interest in external dialysis as a means of treating renal insufficiency in humans has been revived, and this interest has been fostered largely through the work of Kolff and co-workers,^{41,42} Murray, and Alwall, all of whom, working independently, have further developed the "artificial kidney." These three machines, while differing in construction and in operational details, employ essentially the same fundamental principles. All three utilize as a dialyzing membrane cellophane tubing wound around a cylinder immersed in a tank containing a physiologic solution. Heparinized uremic blood is passed from a cannula in an artery (Kolff,⁴² Alwall) or a vein (Murray), through the apparatus, and blood purified by dialysis is pumped back into the body by means of a cannula in one of the peripheral veins.

INTERNAL DIALYSIS GASTRO-INTESTINAL TRACT

Utilization of different portions of the gastro-intestinal tract for dialysis has been attempted by numerous investigators. Ochsner, and Vermooten and Hare, have reported that by continuous gastric lavage, they were able to remove substantial quantities of urea with subsequent decrease of blood urea nitrogen levels and restoration of normal or near normal electrolyte balance in azotemic patients. Bliss, Kastler and Nadler were able to demonstrate considerable amounts of urea in the vomitus of uremic animals. However, they expressed the opinion that the prospect of gastric lavage as a satisfactory means of extrarenal excretion is not encouraging since, although sizable quantities of urea and other metabo-

lites can be removed by this route, in cases of uremia nitrogen accumulation exceeds the maximal rate of removal

Goudsmit passed a modified multiluminal tube of the Miller-Abbott type into the upper part of the jejunum in 3 volunteer normal human subjects and in 2 patients with far-advanced renal insufficiency. A balloon placed immediately proximal to the tip was then inflated and a hypertonic solution of sodium sulfate was introduced at regular intervals through the tube. The average volume of fluid removed was 655 cc per hour in the normal subjects and 399 cc per hour in the patients. Average urea concentration of the fluid removed was 93 per cent of that in the blood in normal subjects and 75 per cent in the patients. In one patient, 3,300 cc of fluid, containing more than 10 gm of urea, were removed in the period of one hour. No significant changes were noted in the concentration of urea in the blood. Auguste concluded after duodenal drainage in a series of patients suffering from uremia that the volume of duodenal fluid in the uremic patient exceeds by one and a half to two times that in a normal subject, and that both the chloride and urea concentrations were higher in such fluid. In this manner, he treated 4 uremic patients suffering from far advanced chronic nephritis regarding the drainage four hours daily over a long period. In all cases there was noticeable clinical improvement with lowering of blood urea levels, although the amount of urea removed in this manner varied between 1.0 and 1.5 gm daily.

White and Harkins, after continuous irrigation with hypertonic fluids of isolated high intestinal loops in 10 cases of uremia by bilateral nephrectomy, found that this procedure resulted in the removal of 1.5 to 2.5 gm of urea but did not appreciably prolong the life of the animal, although the average terminal blood urea nitrogen was lowered by about 26 per cent. The amount of urea nitrogen removed varied from 1.5 to 2.5 gm per hour. The irrigated per hour. P. C. Harkins and J. H. White, using a multiluminal tube similar to the Miller-Abbott tube, attempted continuous irrigation of the small intestine in nephrectomized animals. A small amount of reduction of blood urea was observed in some cases.

liters of perfusing fluid were used over a six hour period, and found the rinsing fluid after perfusion to contain 4.3 to 5.4 gm of nonprotein nitrogen

Fine, Frank and Seligman tried continuous irrigation of a loop of ileum in one of their cases, but found so poor a clearance of blood urea by this means that they estimated that perfusion of a loop 200 inches (5 meters) long would be required to achieve a blood urea clearance of 10 cc per minute, the approximate clearance necessary to avoid the development of uremia. Perfusion of magnesium sulfate in 50 per cent solution through the loop was ineffective in increasing fluid and urea output, and resulted in nausea and vomiting. Kolff³⁹ has attempted a similar procedure and reported more favorable results. He found that the urea concentration in the perfusion fluid varied inversely with the rate of flow of fluid through the intestinal loop. With a rate of flow of 1,000 cc per hour, an average excretion of urea of 0.48 gm per hour was obtained, although there was a gradual rise of the blood urea level.

Oppenheimer and Rosenak have reported a case recently in which irrigation of the upper part of the small intestine was performed through a Miller-Abbott tube weighted at the end, with resultant decrease of blood urea nitrogen from 107 mg per 100 cc before lavage to 46 mg per 100 cc after lavage. We have tried lavage of the small intestine in a severely uremic patient suffering from advanced chronic glomerulonephritis, using a biluminal tube, the inflow lumen being 3 feet and the return lumen 9 feet in length.⁵⁴ Passage of the tube was extremely difficult owing to the patient's irritability and reverse peristalsis of the upper part of the gastro-intestinal tract. Introduction of perfusion fluid into the short lumen, the tip of which was placed in the second portion of the duodenum, invoked vomiting so severe that all except 4 feet (122 cm) of the tube was regurgitated into the stomach. Further, although continuous suction was applied to the return lumen, the fluid introduced apparently rapidly passed the distal tip of the tube, for inconsequential amounts of fluid were obtained through suction, whereas the

patient had several copious watery stools immediately after the attempt

Lansberg and Szenkier performed high colonic lavage with tapwater in rabbits made uremic with uranium nitrate. After lavage for thirty minutes, 201 mg of urea were recovered in the washings, with reduction of the blood urea level from 220 to 180 mg per 100 cc of blood. A second uremic rabbit, after lavage for sixty minutes, showed marked recession of uremic symptoms, and the perfusion fluid was found to contain 230 mg of urea. The impression of Lansberg and Szenkier was that the level of urea in the blood does not represent a measure of the severity of uremia, and that the improvement shown resulted, not from the removal of urea, but from removal of large amounts of toxic substances from the colon (cresols, indican) which, they felt, are more important in the pathogenesis of uremia than urea. Kolff²⁹ attempted colonic lavage through an appendical stoma in 2 patients, but found the concentration of urea in the perfusion fluid to be so small as to indicate to him that this method has little practical importance as a method of dialysis. We have tried lavage of the colon in the same manner on a patient suffering from terminal chronic glomerulonephritis, and are in accord with Kolff's observation that the concentration of urea in the washings from the bowel is too small to render this method effective in the treatment of uremia.¹⁸

It is apparent from the foregoing discussion that, while extensive studies, both experimental and clinical have been carried out, there is a wide variation in the results obtained by different investigators using different segments of the gastro intestinal tract. Further study is needed in order to elucidate more clearly the interchange of fluids, electrolytes and other crystalloids across the wall in different segments of the gastro-intestinal tract, and the application of the information thus obtained to the treatment of renal insufficiency.

INTERNAL DIALYSIS: PERITONEUM

The peritoneum has long been recognized as an excellent dialyzing membrane with a filtering surface of approximately

22,000 square centimeters⁶⁶ in the average adult, compared with an approximate glomerular filtering surface of 15,000 square centimeters⁷⁸

Experimental Studies on the Physiology of the Peritoneum.—Since an understanding of the fundamental physiologic principles on which peritoneal lavage is based is of vital importance if all precautions are to be taken to avoid disaster, we believe it is important at this point to review briefly some of the early experimental observations on the physiologic behavior of the peritoneum and some of the experimental studies done on peritoneal lavage as a means of treating urinary suppression and uremia before the practical clinical considerations of the technic are described

It has been shown by von Recklinghausen, Orlow, Hertzler, Clark, Putnam, Darrow and Yannet and others^{13 33,38} that crystalloids, as well as particulate matter such as India ink, certain dyes, milk, bacteria and erythrocytes, are freely absorbed from the peritoneal cavity Von Korányi, and Meltzer and Salant, noted increased rates of absorption from the peritoneal cavity in uremic animals, and were able to demonstrate increased osmotic pressure of the blood of such animals Fleischer and Loeb¹⁹⁻²¹ found that anything which increased the osmotic pressure of the blood increased the rate of absorption of crystalloids and water from the peritoneal cavity

Orlow observed that injection into the peritoneal cavity of solutions containing 0.3 per cent sodium chloride resulted in an increase of salt content although the solutions decreased in volume Salt solutions of a concentration of 1.5 per cent or more caused a marked transudation of fluid from the blood stream but a rise of plasma chlorides Solutions containing 0.4 to 1.5 per cent of sodium chloride diminished in volume in three hours and tended to approach the chloride concentration of blood serum Intravenous injection of hypertonic salt solutions hastened absorption of peritoneal fluid and diffusion of salt from the blood stream

Clark demonstrated that the rate of absorption of a substance across the peritoneal membrane is proportional to the rate of diffusion of that substance When a solution of sodium chloride was introduced, because the rate of diffusion of chlo-

ride is greater than the average rate of diffusion of the constituents of the blood, a fairly rapid rate of absorption of fluid occurred early, whereas, later, various slowly diffusible substances entered the peritoneal fluid from the blood stream, and as the osmotic pressure of the peritoneal fluid increased, absorption of water became slower. On the other hand, if glucose, which has a low rate of diffusion, was introduced, since the rate of diffusion of the substance in the peritoneal cavity was lower than that of the constituents of the blood, crystalloids entered the peritoneal fluid more quickly than they left it, and the osmotic pressure of the peritoneal fluid increased. Because of this, little or no absorption of fluid occurred. Clark also showed that the rate of absorption of solutions across the peritoneum was increased by a warm solution and was retarded by a cold solution. This phenomenon he ascribed to dilatation of blood vessels increasing the efficiency of the dialyzing membrane. He was not able to demonstrate any difference in the rate of absorption of acid, neutral or alkaline solutions.

Putnam has shown that solutions of sodium chloride of less than 1 per cent concentration are tolerated well by experimental animals, although they may be uncomfortable for an hour or two, vomit frequently and pass large quantities of urine. Such solutions show progressive decrease of volume and contain various crystalloids such as urea and glucose, whereas the chloride concentration tends to approach that of blood plasma. Hypertonic solutions of sodium chloride, in concentrations greater than 1 per cent, were found to be tolerated poorly and were painful. Animals receiving hypertonic solutions passed large quantities of urine and frequently died within two hours showing at autopsy subcutaneous edema, dilated hearts, wet lungs and marked injection of the peritoneum.

Schechter, Cary, Carpentieri and Darrow injected various solutions intraperitoneally and analyzed the changes in composition of these solutions at the end of a specified time. After the injection of 0.9 per cent solution of sodium chloride, they found that the content of total base remained constant, the amount of chloride decreased, and bicarbonate appeared in the

fluid When a solution of sodium chloride, sodium bicarbonate and potassium in proportions resembling that of interstitial fluid was used, they noted a slight decrease of bicarbonate and the appearance of undetermined acid ions Hartmann's solution changed in that the lactate content decreased as the amount of bicarbonate increased

Darrow and Yannet later studied the effects of intraperitoneal injection of a 5 per cent solution of glucose The solution changed less than 10 per cent in volume during the observation period of three to six hours There was, however, a reduction of plasma volume as evidenced by a concentration of plasma protein There was also a reduction of plasma chlorides and sodium, as well as a reduction of protein concentration in the erythrocytes with very little change of total body water Symptoms and signs of dehydration appeared Darrow and Yannet felt that this phenomenon was due to shift of extracellular water into cells, producing dehydration of the extracellular fluids and hydration of the intracellular space produced by loss of salt from the plasma into the peritoneal cavity When a 1.8 per cent solution of sodium chloride was injected, there likewise was little change in the volume of peritoneal fluid at the end of the observation period There was, however, increase of extracellular electrolytes with little change of body water and few symptoms except thirst Furthermore, there was found to be an increase of plasma volume accompanied by an increase of the concentration of chlorides and sodium in the blood serum, decrease of plasma protein, and increase of concentration of protein in erythrocytes owing to loss of cellular water This they explained on the basis of a shift of water from cells into extracellular spaces producing dehydration of cells and hydration of extracellular fluids

Curtis and Pacheco perfused distilled water and other chloride-free fluids through the peritoneal cavity of rabbits The use of distilled water increased the respiratory rate within one hour, followed by generalized muscular twitching, convulsions, anuria and death of the animal within two to five hours There was marked depletion of plasma chlorides, the carbon dioxide combining power of the plasma decreased, with a rise of the urea and nonprotein nitrogen levels fol-

lowed by oliguria and anuria. There was no evidence of hypoglycemia and the addition of 0.12 per cent of glucose to the perfusate was of no benefit. When Ringer's solution with glucose was used, there were no muscular twitchings or convulsions, and after eight to nine hours of perfusion the animals were in good condition. Plasma chlorides were elevated and there was a continuous flow of urine. The use of 0.9 per cent solution of sodium chloride maintained the animals in good condition, there was a continuous flow of urine, the plasma chloride and carbon dioxide combining power remained within normal limits, and there was slight decrease of nonprotein nitrogen and urea levels in the blood. The use of 4.2 per cent of glucose produced hypochloremia and hyperglycemia with similar symptoms to those induced by the use of distilled water. The addition of 0.45 per cent of sodium chloride to the solution resulted in a rise of plasma chlorides and marked symptomatic improvement. Curtis and Pacheco concluded that the loss of sodium chloride was a factor of prime importance in the development of a fatal outcome from hypochloremia and stated that this could be blocked by adding sodium chloride in proper concentration to the perfusate or by giving it intravenously.

From the foregoing experimental data, it will be seen that regardless of whether a natural or an artificial membrane is used, the composition of the fluid with which it is in contact is of the utmost importance, since, according to the physical properties of membranes, each crystalloid substance diffuses through the membrane from the side of higher concentration to the side of lower concentration. It is a common belief that fluids and crystalloids enter the cell by osmotic diffusion until osmotic balance is reached. However, it is well known that absorption takes place through the cell membrane and not through the cells themselves. Consequently, the degree of absorption is determined by the degree of osmotic balance and diffusion, and not by the degree of osmotic balance alone. The degree of osmotic balance is determined by the degree of diffusion out of the cell and the degree of osmotic balance in the perfusate. The degree of osmotic balance in the perfusate is determined by the degree of osmotic balance in the plasma. The degree of osmotic balance in the plasma is determined by the degree of osmotic balance in the blood.

water will diffuse into the blood, and if it is made hypertonic, water will leave the blood

Putnam stated that the living peritoneum resembles essentially a dialyzing membrane with holes punched in it which permit a seepage of larger molecules than usually would diffuse through a dialyzing membrane and that the diffusion of molecules through the peritoneum occurs more rapidly than with ordinary dialyzing membranes. This seepage occurs more readily in the direction of the blood plasma than in the direction of peritoneal fluids. If one adds to this the experience of Fleischer and Loeb¹⁹⁻²¹ that peritonitis alters the direction and rate of flow by introducing the complicating factor of transudation or exudation, plus the fact that uremia is accompanied by an increased osmotic pressure in the blood which hastens absorption from the peritoneal cavity, one has a fairly comprehensive picture of the peritoneum as a dialyzing membrane, and of the complexity of the problems involved in maintaining correct fluid and electrolyte balance in the body.

Obviously, then, the success of any artificial kidney will depend, not only on the practicability of the mechanical arrangements, but also on the compounding and use of a suitable perfusing fluid.

Experimental Studies on Peritoneal Lavage in the Treatment of Uremia.—Earlier investigators who used the peritoneum as a dialyzing membrane failed both experimentally and clinically in the treatment of uremia, largely because of a poor choice of solutions. Many attempts had been made to treat both experimental animals and uremic patients by peritoneal lavage but results to date have been only partially satisfactory, apparently largely owing to the fact that water and electrolyte balances were not sufficiently considered.

Rosenak and Siwon in 1926 made dogs uremic by nephrectomy and noted great decrease of blood nitrogen levels and distinct clinical improvement after lavage of the peritoneum with 5 per cent solution of glucose. They felt that results obtained were more favorable than those obtained from dialysis of blood through a dialyzing membrane outside the body. Von Jenev concurred in the findings of Rosenak and Siwon.

but learned that sodium chloride solution was needed in place of glucose for transperitoneal dialysis in order to check further loss of chloride in a clinical condition (uremia) already associated with depleted plasma chlorides due to vomiting and diarrhea. Similar results could be obtained by using the same solution as Rosenak and Siwon had used and replacing depleted plasma chlorides by the parenteral route.

Bliss, Kastler and Nadler made animals uremic by nephrectomy, ureteral ligation or administration of uranium nitrate. They introduced 750 cc of a solution of balanced salts into the peritoneal cavity, allowed it to remain ten minutes and then allowed it to flow out by gravity. Five to twenty washings were carried out in one experiment and at the termination of the experiment there had occurred prompt and dramatic decrease of nitrogen retention, in one animal from 160 to 80 mg per 100 cc in three hours. Some of the treated animals died, apparently from massive peripheral and pulmonary edema. Bliss and his associates were able to identify urea, sulfate, phosphate, creatinine, excessive amounts of chloride and traces of protein in the perfusing fluid recovered.

Haam and Fine repeated the experiments of Bliss and Nadler after rendering rabbits anuric by administration of mercuric chloride. No hydremic changes in the blood were observed, although the weight of the animals decreased slightly during the experiment. Observations on the nitrogen levels in the blood after the experiment demonstrated that the maximal diffusion of urea from the dialysate fluid occurs in two to four hours and that the rate of diffusion occurs when the blood urea nitrogen is significantly elevated.

Seligman, Frank and Farnham have reported on peritoneal irrigation in a series of experiments. They found that the clearance of urea by peritoneal dialysis is directly proportional to the rate of irrigation. They also found that the clearance values for urea are lower than those for inulin, indicating that urea is reabsorbed in the peritoneum. They also found that the clearance of urea is increased by the use of a larger volume of dialysate and by the use of a higher flow rate.

the animal in the supine position. They found urea clearance values after irrigation of different segments of the gastrointestinal tract to be best in the jejunum, amounting there to about 10 per cent of renal function, whereas irrigation of the pleural cavity resulted in a blood urea clearance of about a third that obtained by peritoneal lavage.

Abbott and Shea have carried out extensive investigations on nephrectomized animals in an attempt to determine (1) whether continuous or intermittent lavage was most efficient, (2) in the case of the latter method, how long fluid should remain in the peritoneal cavity, the best method of injection, and the optimal frequency of injections, and (3) the selection of a proper solution. Their studies substantiated data previously reported by others in that the use of solutions not containing sodium chloride resulted in severe depletion of plasma chlorides, evidence of dehydration, hemoconcentration and shock, whereas use of fluids in which the chloride concentration was greater than that of normal blood plasma resulted in increase of plasma chlorides, depletion of plasma carbon dioxide combining power, evidence of hemodilution and edema. Their studies revealed that intermittent injection and withdrawal of a solution having a chemical composition similar to that of interstitial fluid made hypertonic by the addition of dextrose were most desirable, a trocar being used through which a rubber catheter could be introduced.

Clinical Observations on Peritoneal Lavage.—Ganter in 1923 was the first to employ peritoneal lavage, "internal dialysis," clinically, as a means of treating renal insufficiency, and a number of reports of similar clinical trials have appeared in the literature since that time. Within the past two years, there has been increasing interest in this procedure by both physiologists and clinicians, owing largely to the impetus of the excellent experimental and clinical reports of Fine, Frank and Seligman.^{18, 22}

Indications—Indications for the use of peritoneal lavage are those situations associated with acute urinary suppression on the basis of temporary renal damage. Transfusion with incompatible blood, sulfonamide intoxication, severe burns, poisoning with heavy metals or other drugs, toxemia of preg-

nancy, the "crush injury syndrome," hemolytic reactions, shock, certain urologic and surgical procedures all may produce acute renal failure and uremia which should be amenable to artificial removal of waste products with ultimate recovery of the patient. Acute glomerulonephritis and acute pyelonephritis with anuria may in some instances be included in this category. Recently, it has been shown that methyl alcohol diffuses readily across the peritoneum and peritoneal lavage therefore has been suggested as a method for the treatment of acute methyl alcohol intoxication.⁷ From the standpoint of therapeutic value, patients who have renal failure and uremia secondary to advanced organic renal parenchymal damage should be considered as unsatisfactory candidates for peritoneal lavage, because, although temporary alleviation of symptoms with regression of laboratory evidence of azotemia may occur during the lavage period, signs and symptoms of progressive renal failure and uremia again ensue as soon as the procedure is terminated. The intrinsic risk and hazards attending the procedure are sufficiently great to make its justification for use in such cases debatable.

Review of the Literature — Prognosis — Insofar as we have been able to determine, data on 53 cases of renal insufficiency and uremia in which peritoneal lavage was attempted have been reported in the literature from 1923 to date (table 1) although undoubtedly there have been unreported instances in which peritoneal lavage has been tried, either successfully or unsuccessfully. Of the 53 patients, 13 had serious organic disease with advanced irreversible renal damage as indicated by the diagnosis. Eleven of the 13 died soon after peritoneal lavage was instituted and the fate of 2 is unknown although with the diagnoses stated one would assume an ultimately fatal outcome. In 13 cases, the diagnosis is unknown although the outcome in 10 of these has been reported as unsuccessful. In the 27 remaining cases in which the diagnosis indicates possibly reversible renal impairment, 13 recoveries have been reported (48 per cent).

Nitrogen Excretion — Of the 53 cases reported, intermittent lavage has been employed in 27 cases with lavage periods of two to eight hours' duration, repeated in some cases three to

TABLE 1
CASES OF PERITONEAL LAVAGE REPORTED IN THE LITERATURE

Year	Author	Cases	Diagnosis	Outcome
1923	Ganter	1	Chronic nephritis	Died
1927	Heusser and Werder	3	Not stated Not stated Not stated	Died Died Died
1934	Balázs and Rosenak	2	Mercuric chloride poisoning* Mercuric chloride poisoning	Died Died
1938	Wear Sisk and Trinkle	5	Carcinoma of bladder Carcinoma of bladder Hypertrophied prostate, obstruction Bilateral hydronephrosis Renal and vesical calculi	Died Died Died Died Recovered
	Rhoads	2	Diabetes chronic nephritis Renal calculus advanced nephritis	Died Died
1946	Fine Frank and Seligman ^{18 22}	4	Carcinoma of cervix ureteral obstruction Transfusion with incompatible blood Transfusion with incompatible blood Sulfonamide intoxication	Died Died Died Recovered
	Weiss and Mills	1	Hypertensive cardiovascular renal disease	Died
	McGraw and others	1	Chronic nephritis	Unknown
	Reid Penfold and Jones	1	Transfusion with incompatible blood	Recovered
1947	Smith and Eaves	4	Transfusion with incompatible blood Postoperative hemolytic reaction Sulfonamide intoxication Prostatitis; oliguria	Recovered Died Recovered Recovered
	Goodyear and Beard	1	Transfusion with incompatible blood	Recovered
	Muirhead and others ^{17 49}	3	Transfusion with incompatible blood Postoperative hemolytic reaction Transfusion with incompatible blood and postoperative shock	Recovered Died Unknown
	Robertson and Rutherford	1	Transfusion with incompatible blood	Died
	Backley and Scholten	1	Mercuric chloride poisoning	Died
	Stream, Korenberg and Portnuff	1	Transfusion with incompatible blood	Recovered
	Grossman Ory and Willoughby	1	Toxemia of pregnancy	Recovered
	Doenges and Strahan	1	Sulfonamide intoxication	Recovered
	Connolly and Lempka	2	Chronic ulcerative colitis; transfusion with incompatible blood Sulfonamide intoxication	Died Died
	Bassett and others	1	Subacute glomerulonephritis	Died
	Kolff ²³	13	Bilateral renal calculi with renal scarring Bilateral contracted and calcified kidneys Chronic nephritis 10 cases not stated	Unknown Died 7 died 3 recovered
1948	Authors	4	Carbon tetrachloride intoxication Post-transurethral oliguria Transfusion with incompatible blood Indeterminate postoperative anuria	Died Recovered Recovered Died
Total number of cases reported to February 1 1948 = 53				
Reversible lesions	27	Patients died	34	
Irreversible lesions	13	Patients recovered	16	
Indeterminate lesions	13	Outcome unknown	3	
	53		53	
Recovery rate based on 27 cases with reversible lesions = 48 per cent†				

* Boldface type indicates reversible lesions.

† In the 27 cases with reversible lesions there were 13 recoveries

six times daily. In the remaining 26 cases, continuous lavage has been used, the lavage period varying from two to twenty-one days. Table 2 gives a partial list of cases in which information regarding blood nitrogen levels and nitrogen excretion is reported. It is of interest that the average decrease of the levels of nonprotein nitrogen or urea in the blood during the lavage periods in cases in which intermittent lavage was used, was 47 mg per 100 cc, whereas in cases in which continuous lavage was used, the average decrease of blood urea or blood nonprotein nitrogen levels during the lavage period was 91 mg per 100 cc. This would tend to indicate that insofar as nitrogen elimination is concerned, continuous lavage is preferable to intermittent lavage periods of shorter duration. Perusal of the data in table 2 leaves no doubt that peritoneal lavage is an effective means of removing stored metabolic waste products from the blood and tissues of the uremic patient, for in most instances the procedure has resulted in marked decrease of blood urea or nonprotein nitrogen levels, with recovery of large amounts of nitrogen in the perfusing fluid.

Solutions Used—Various solutions have been used for peritoneal lavage, some of which, though generally considered to be physiologic solutions, appear to be unsatisfactory for peritoneal lavage, in the light of previous experimental work on the interchange of fluid and crystalloids across the peritoneum. Balázs and Rosenak used 0.8 per cent solution of sodium chloride in one case and 4.2 per cent solution of glucose in another, and Ganter used 0.8 per cent solution of sodium chloride in his case, but information is not available as to the behavior of plasma chlorides and carbon dioxide combining power of the blood or the presence or absence of edema in these three cases. The various solutions which have been employed and the frequency of their use are detailed in tables 3 and 4. These tables are somewhat incomplete owing to the fact that the presence or absence of hyperchloremia, acidosis or edema, either pulmonary or peripheral, is not commented on in all reports. It appears to us, however, to be of major significance that in 8 (41 per cent) of 18 cases in which plasma chloride values were reported, plasma chloride

TABLE 2
NITROGEN EXCRETION ACROSS PERITONEUM

Author	Type of Lavage	Duration Lavage	Solution Used	Blood Non-protein Nitrogen, mg per 100 cc		Total Amount of Nitrogen Recovered in Dialysate
				Before Lavage	After Lavage	
Ganter 1923	Intermittent	1 day, 3x	0.8% NaCl	97	90	
Balázs and Rosenak 1934	Intermittent Intermittent	2 hr 3 hr	4.2% dextrose 0.8% NaCl	182.4 148.8	158.4 139.2	15.7 mg % N 1.28 gm % N
Wear, Sisk and Trinkle 1938	Intermittent Intermittent Intermittent	5 1/4 hr 2 1/4 hr 8 1/4 hr	Hartmann's (pH 3.5) Locke-Ringer (pH 7.6) Locke-Ringer	122 246 151	107 194 111	10.3 gm NPN 3.38 gm NPN 5.9 gm NPN
Rhoads 1938	Intermittent Intermittent	1 day, 6x 3 days	See table 5	184 233*	155 153*	75 mg % urea N 37 gm urea N
Fine, Frank and Seligman 1946	Continuous	5 days	Modified Tyrode's	195	57	82 gm urea
	Continuous	12 days	Modified Tyrode's	145	70	164 mg % urea
	Continuous	7 days	Modified Tyrode's	185	43	12-20 mg urea/day
	Continuous	4 days	Modified Tyrode's	90	42	60 gm urea
Weiss and Maltz 1946	Continuous	4 days		297	126	30-45 mg % urea N
Reid, Penfold and Jones 1946	Intermittent	3 days	1.8% NaCl	255	130	7 gm urea

Smith and Eaves 1917	Continuous	10 days	Hartmann's	110*	78*	±118 gm urea
	Continuous	3 days	Hartmann's + 50% dextrose	109	86*	±60 gm urea
	Continuous	3 days	Hartmann's + 5% dextrose	91*	12	±60 gm urea
	Continuous	2 days	Hartmann's + 2% dextrose	160*	111*	
Goodyear and Beal 1917	Continuous	1 day	Modified Tyrode's	86	30	
	Continuous	12 days	Modified Tyrode's	189†	107†	77 gm urea
Muirhead and others 1917	Continuous	8 days	Modified Tyrode's	211†	122†	115 gm urea
	Continuous	1 day	Modified Tyrode's	171†	22†	71.5 gm. urea
Buckley and Scholten 1917	Continuous	12 days	Modified Tyrode's	109	130	47-53 mg %
	Continuous	10 days	Modified Tyrode's	110	15	
Steen Korenberg and Portnuff 1917	Continuous	3 days	" solution	22†	118	71 1 gm N
	Continuous	14 days	Modified Tyrode's	103	13 6†	13† 6 gm urea
Connolly and Lempek 1917	Continuous	21 days	Modified Tyrode's	135	155	140 82 gm. NPN
	Continuous	8 days	Modified Tyrode's	246†	158†	113 2 gm urea
Bassett and others 1917	Continuous	6 days	P solution	222†	90†	69 3 gm urea
	Continuous	6 days	Modified P solution	198†	58†	60 9 gm urea
Authors 1918	Continuous	6 days	P solution	288†	198†	101 0 gm urea

* Urea nitrogen.

† Urea

TABLE 3
ACID-BASE BALANCE CASES REPORTED IN LITERATURE

Solution	Plasma Chlorides, mg per 100 cc		CO ₂ Combining Power, vol per 100 cc		Edema
	Before Lavage	After Lavage	Before Lavage	After Lavage	
Hartmann's (pH 3.5)	660	587			
Hartmann's					+
Hartmann's +50% dextrose	510	500	56	58	
Hartmann's +5% dextrose					+
Hartmann's +2% dextrose	462	517	11	54	+
Locke Ringer (pH 7.6)			23.8	22.8	0
Locke-Ringer			21	17	0
Locke-Ringer			51	51.3	
Locke-Ringer			11.4	Same	
Rhoads's	591	679	31	29	0
Rhoads's	436		33		0
Sodium chloride 1.8%	470	670			
Modified Tyrode's			20-30	18	+
Modified Tyrode's		660	23	40	+
Modified Tyrode's	538	611	29.2	16.9	+
Modified Tyrode's			39		+
Modified Tyrode's	360	611	46	30	+
Modified Tyrode's	501	591	62	26	+
Modified Tyrode's	307	613	50.1	33.7	
Modified Tyrode's	520	690			+
Modified Tyrode's			40	20	+
Modified Tyrode's			37		+
Modified Tyrode's	562	585	27	62	+
Modified Tyrode's	179	672	51.1	11.9	+
"A" solution	163	535	36.2	39.3	0
'A" solution	250	510	57.5	11	+
"P" solution	135	565	38.2	55.1	0
'P" solution	524	602	17.5	55.1	0
Modified "P" solution	100	518	73	61.5	+

TABLE 1
ACID-BASE BALANCE CASES REPORTED IN LITERATURE

Solution	Total Cases	Hyperchloremia				Acidosis				Edema			
		Chlorides Reported	Yes	No	Yes %	CO ₂ Reported	Yes	No	Yes %	Reported	Yes	No	Yes %
0.8% NaCl	2												
1.2% dextrose	1												
Hartmann's	1	3	0	3	0	2	0	2	0	3	3	0	100
Locke-Ringer	1					1	3	1	75	2	0	2	0
1.8% NaCl	1	1	1	0	100								
Rhoads's	2	1	1	0	100	2	2	0	100	2	0	2	0
Modified Tyrodes	16	8	6	2	75	9	6	3	67	11	11	0	100
A	2	2	0	2	0	2	0	2	0	2	1	1	50
P	2	2	0	2	0	2	0	2	0	2	0	2	0
Modified P	1	1	0	1	0	1	0	1	0	1	1	0	100
Kolff's (see table 2)	13												
Unknown	4												
Total	53	18	8	10	11	22	11	11	50	23	16	7	70

levels greater than normal (103 milliequivalents per liter) developed during the lavage period. Of 22 cases in which values for plasma carbon dioxide combining power were given, 11 (50 per cent) were reported as showing decrease in the levels of carbon dioxide combining power of the plasma during the lavage period to less than normal (27 milliequivalents of HCO_3^- per liter). In 16 (70 per cent) of 23 cases in which the presence or absence of edema was noted, clinical edema, either pulmonary or peripheral, developed during the lavage period. The electrolyte balance of normal blood plasma may be found in figure 134.

Chloride Balance—When one examines tables 3 and 4 it will be noted that three solutions used in the series have been responsible for the 8 cases in which abnormally high plasma chlorides developed. These solutions are 1.8 per cent saline solution, the solution used by Rhoads, and modified mammalian Tyrode's solution. Table 5 gives the composition of these various solutions. It will be noticed that in these three solutions the chloride content is excessive as compared with that of blood plasma (307.7, 255.0, and 145.0 milliequivalents per liter, respectively). One could expect then that when any of these solutions is perfused through the peritoneal cavity, diffusion of excessive amounts of chloride and sodium across the peritoneal membrane will result, with hyperchloremia and hypernatremia.

Acidosis—It will be noted in tables 3 and 4 that three solutions account for the 11 cases of acidosis with values for the plasma carbon dioxide combining power below normal. These solutions are Locke-Ringer solution, Rhoads's solution and modified Tyrode's solution. This can be explained easily on the basis of two facts: (1) all three solutions contain a higher concentration of chloride than blood plasma (162 to 165, 255.0 and 145 milliequivalents per liter) and (2) all three solutions are deficient insofar as bicarbonate is concerned (Ringer's 3 milliequivalents of HCO_3^- per liter, Locke's 2 milliequivalents of HCO_3^- per liter, Tyrode's, 12 milliequivalents of HCO_3^- per liter). Thus chloride diffuses from the peritoneal cavity into the circulating blood, whereas bicarbonate diffuses from the blood stream into the peritoneal

TABLE 5
COMPOSITION OF VARIOUS SOLUTIONS USED FOR PERITONEAL DIALYSIS

Solute, gm. per liter	Winger's Solution	Locke's Solution	Tyrode's Solution	Modified Tyrode's Solution	Rhoads's Solution	Hart- mann's Solution	Kolff's Solution	A's Solu- tion	P Solu- tion	Modified "P" Solution
Sodium chloride (NaCl)	9.0	9.0	9.0	8.0	11.5	6.0	6.0	6.1	6.0	6.0
Potassium chloride (KCl)	0.3	0.24	0.2	0.2	0.1	0.3	0.1	0.35	0.2	0.2
Calcium chloride (CaCl ₂)	0.25	0.12	0.2	0.1	0.2	0.2	0.28	0.23	0.1	0.1
Magnesium chloride (MgCl ₂)			0.1	0.1				0.05	0.1	0.1
Sodium acid phosphate (NaH ₂ PO ₄)			0.05	0.05				0.07	0.05	0.05
Sodium bicarbonate (NaHCO ₃)	0.2	0.2	1.0	1.0			2.0	2.20	3.0	2.0
Sodium lactate (NaC ₃ H ₅ O ₃)					2.40	3.1				
Sodium citrate (Na ₃ C ₆ H ₅ O ₇ · 3H ₂ O)										1.57
Phosphate		1.0	1.0	1.5			10-30	10-20	20	20

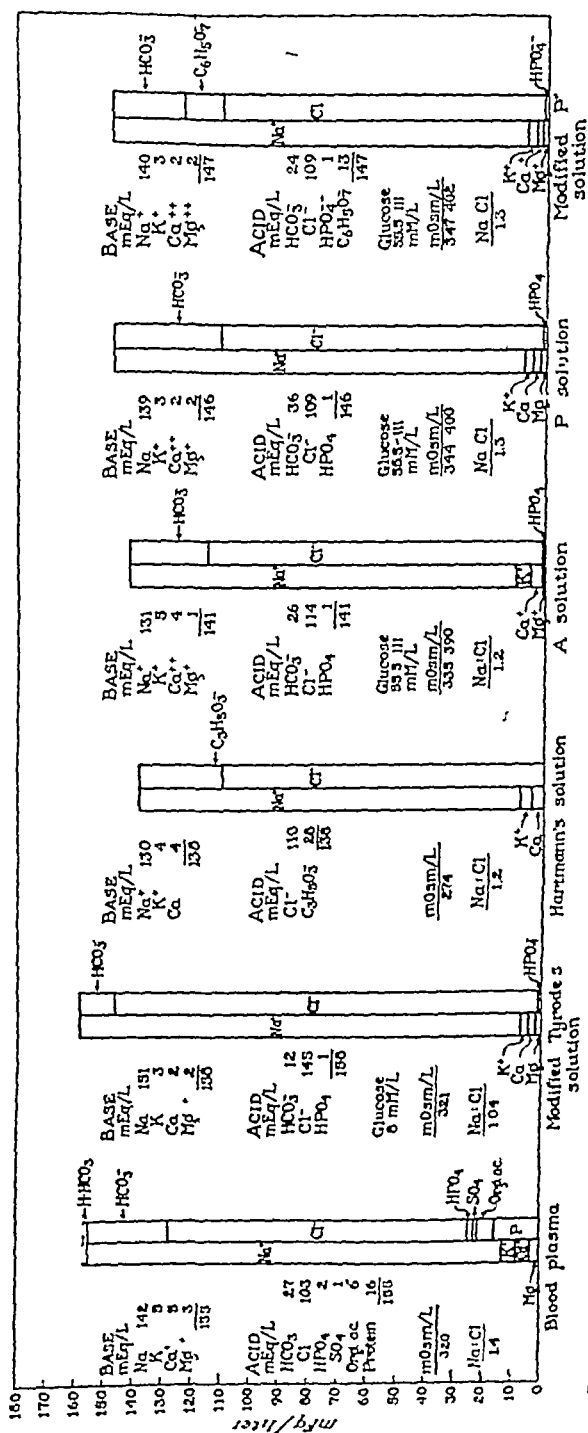


Fig 131—Acid-base composition of normal blood plasma and of various solutions employed for peritoneal lavage (After Gamble, J L Chemical anatomy, physiology and pathology of extracellular fluid a lecture syllabus. Cambridge, Massachusetts, Harvard University Press, 1917)

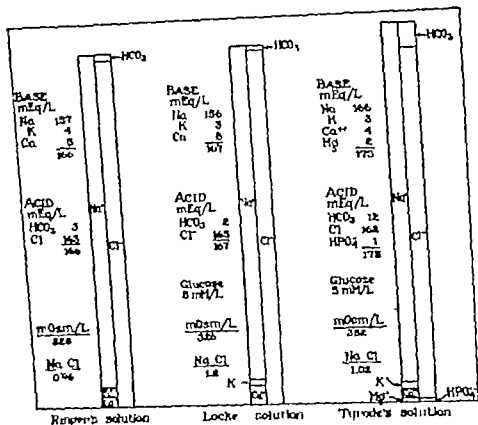


Fig 131 (Continued) — Acid-base composition of normal blood plasma and of various solutions employed for peritoneal lavage.

fluid. Although Rhoads's solution contains sodium lactate, it is probable that the amount of lactate absorbed from the peritoneal fluid breaks down at too slow a rate to make sufficient base available to offset the loss of bicarbonate.

Edema—Further examination of tables 3 and 4 reveals that four solutions were responsible for the 16 cases reported in which edema, either pulmonary or peripheral, was observed. It is significant that of this number modified Tyrode's solution was used in 11 cases. This solution, although iso-osmolar with blood plasma (321 milliosmols per liter), has been shown not to be in electrolytic balance with blood plasma insofar as chloride and bicarbonate are concerned. The excellent work of Darrow and Yannet described earlier in this discussion may offer a logical explanation for the manner in which modified mammalian Tyrode's solution may contribute to the development of edema. Furthermore if, as has been reported previously¹⁹⁻²¹ the blood of uremic patients has a higher osmotic pressure than that of normal persons, the modified Tyrode's solution, iso-osmolar with normal plasma, becomes hypo-osmolar in the presence of uremia.

The appearance of edema in cases of uremia has been reported by

solution was used may be due to the fact that Hartmann's solution has an osmolar concentration of 274 as against 320 for normal plasma (fig 134) This discrepancy, as in the case of modified Tyrode's solution, becomes greater in the presence of uremia Since Hartmann's solution appears to be otherwise essentially in equilibrium with blood plasma, this tendency could be offset by the addition of enough dextrose to render it hyperosmolar, as has been done in the case of "A" solution¹ and "P" solution⁵⁷ (table 5 and fig 134) In one of our cases a transient episode of pulmonary edema developed during lavage with modified Power's solution The cause for this episode appears to us to be clear and will be discussed in greater detail later We can offer no explanation on the basis of the composition of the dialysate for the appearance of edema in one of the cases in which "A" solution was used It may have been due to hydremia induced by excessive parenteral administration of fluid or it may have been on the basis of hypoproteinemia

The inaccuracy of the figures in tables 3 and 4 is recognized, and it is probable that if similar data were available for all cases in the series, the figures would be somewhat different Another factor in the inaccuracy of the figures is the impossibility of estimating in all cases the effect on the blood values of parenteral administration of various electrolytes, notably sodium chloride solution and bicarbonate or lactate However, it is our opinion that these data are sufficiently significant to indicate the importance of using a carefully selected lavage solution

METHOD

Choice of Solution —It becomes apparent that any solution, in order to be considered as a suitable perfusing fluid should meet certain qualifications 1 Its composition should be such that it will not alter the normal electrolyte pattern of the plasma and extracellular fluid 2 It should permit a maximal diffusion of nitrogenous and other waste products of a crystalloid nature into it 3 Its tonicity should be such as to insure, insofar as possible, against water exchange across the peritoneum In fact, the ideal fluid should be moderately

hypertonic, for mild dehydration is much less hazardous and more easily controlled clinically than are excessive hydration and edema. 4 The solution should be as nonirritating to the peritoneum as possible, in order to reduce hyperemia and exudation with decrease in the efficiency of the filtering membrane.

Four solutions appear to us to fulfill the foregoing criteria essentially. Hartmann's solution, Kolff's solution,²² the "A" solution of Abbott and Shea, and "P" solution (table 5). In our third case, we used a modification of "P" solution, which will be discussed in the report of that case. These solutions satisfactorily fulfill the first two qualifications. Hartmann's solution as such does not adequately answer the third requirement, but if sufficient dextrose is added to make a 2 per cent solution, its tonicity is sufficiently increased to make it adequate. In regard to the last criterion, any chemical solution introduced into the peritoneal cavity will induce some degree of irritation. This, however, can be kept at a minimum by buffering the solution to a pH approximating that of the blood plasma. Rosenak has stated that too alkaline a solution is as irritating to the peritoneum as one which is too acid.

Preparation of Solution—In our opinion, the irrigating fluid of choice is "P" solution (table 5) which is prepared in large volumes in the following way. Our containers have been balloon flasks of 10 liter capacity instead of 20 liter carboys as suggested by Fine, Frank and Seligman, because the 10 liter flasks are more easily autoclaved and are more easily transported. Nine and a half liters of triple distilled sterile water are run into a sterile 10 liter balloon flask. With the exception of the sodium bicarbonate all the salts and the dextrose for 10 liters of perfusing fluid are dissolved in this water and autoclaved for one hour at 250° F. under 15 pounds of steam pressure. It is important not to autoclave the bicarbonate with the other salts and dextrose since bicarbonate breaks down under such circumstances and calcium and magnesium salts may be precipitated out of the solution. After the solution has been autoclaved for the required time the flask is allowed to cool and when it has reached room temperature sodium bicarbonate from sterile ampoules is added.

7.5 per cent solution) is added in sufficient quantity to produce a bicarbonate concentration of 300 mg per 100 cc (30 gm in 10 liters)

Penicillin is added in a concentration of 10,000 units per liter in an attempt to inhibit contamination of the fluid and bacterial growth in the peritoneal cavity. A sterile solution of heparin is added to inhibit the formation of fibrin on the peritoneal surface. However, Bloor and his co-workers recently have reported that in rabbits given heparin in large doses intraperitoneal adhesions are as likely to develop after peritoneal injection of saline solution or gelatin as in those animals not treated.⁹ We have added heparin in the dosage of 1 mg per liter and have found that the drug in this concentration is not absorbed to a degree sufficient to alter the coagulation time of the blood. Doenges and Strahan added heparin to their solution in the dosage of 2 mg per liter, apparently without untoward effect. Fine, Frank and Seligman added sodium sulfadiazine to their solution in the dosage of 60 to 120 mg per liter. We have omitted sulfonamide compounds from our solution because of the remote possibility of inflicting further injury on an already damaged pair of kidneys. It appears to us that the addition of streptomycin in the dosage of 20,000 units per liter is indicated as prophylaxis against the growth of gram-negative organisms, which are not sensitive to penicillin.

Protein has been recovered from the perfusing fluid in sizable amount and this fact, in association with decrease of the value of plasma protein levels, raises a logical supposition that the patient may be losing protein from the plasma across the peritoneum into the dialysate. For this reason, some have added substances such as gelatin, pectin or acacia to the dialysate, thereby raising the colloidal osmotic pressure of the dialysate in an effort to block loss of protein. The question whether protein molecules can diffuse across the peritoneum has been debated for a long time. Up to the present it cannot be said definitely whether protein actually is lost from the body during lavage or whether protein found in the irrigating fluid is a result of inflammatory reaction on the peritoneal surface itself. We have not added such substances to

the perfusion fluid in any of our cases, but when plasma protein values have decreased, whether owing to protein loss or to inanition we have preferred to use parenteral replacement therapy in the form of blood plasma, serum albumin, whole blood or protein hydrolysates

As a final step in the preparation of the lavaging fluid, "p" solution the pH of which is 8.4 is adjusted to a pH of 7.5 by the addition of chemically pure citric acid

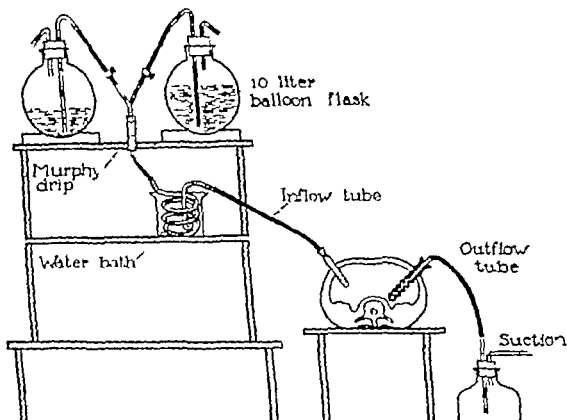


Fig 135—System used for continuous peritoneal lavage

Apparatus—The mechanical arrangement for continuous peritoneal irrigation has been constructed in several ways, but in general the working principle of all devices has conformed to the diagram shown in figure 135, which is a modification of that described by Fine Frank and Seligman. It was necessary for our needs to have a setup which could be easily transported and which would occupy a minimal amount of space. Accordingly we have a setup as shown in figure 136. The box is 31 inches (86 cm) high, and when set on the dresser in a hospital room, the height of the balloon flasks atop the box is about 70 inches (178 cm) above the floor and approximately 36 inches (91 cm) above the patient.

The irrigating fluid flows by gravity from the elevated

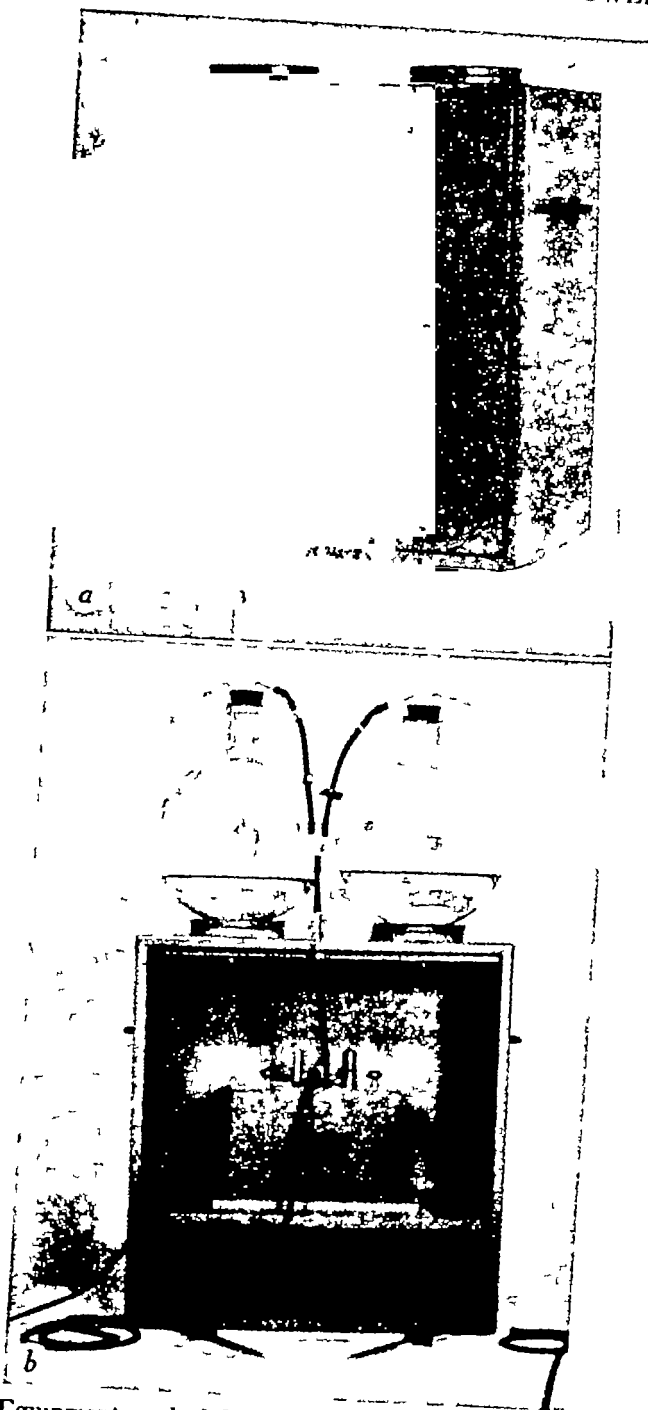


Fig 136—*a*, Equipment packed for transportation *b*, Equipment assembled and ready for use

balloon flasks through siphon tubes, joined by a Y tube, through a drip bulb, then to a glass coil immersed in a constant temperature water bath and from there to the peritoneal inlet tube. The outflow tube is connected by a long section of rubber tubing to a constant suction apparatus and constant suction of 90 to 120 mm. of mercury is maintained.

Our water bath consists of a pancake type heater in an insulated tank covered by a lucite lid into which has been mounted a thermostat of the thermocouple type. The thermostat has been adjusted to maintain the temperature of the water bath at 43°C , which will insure delivery of the fluid to the peritoneal cavity at approximately body temperature (37°C). However, a satisfactory water bath may be devised by coiling the tubing in a large beaker on a hot plate with a simple thermometer to register the temperature of the bath. Clark has shown that rate of absorption of crystalloids and water varied with the temperature of the perfusing fluid. At a temperature of 15°C or more the absorption of sodium chloride and water was greater than at a temperature of 37°C and when the temperature was reduced to 25°C absorption was greatly diminished.

Ime, Frank and Seligman^{18, 22} and others have interposed a Mandler (Berkefeld) filter in the system between the reservoir of solution and the water bath as further prophylaxis against peritoneal infection. We have omitted the bacterial filter from our system for four reasons: 1. Such a filter materially interferes with maintenance of an adequate rate of flow of lavage fluid into the peritoneal cavity. 2. After a period of several hours of continuous lavage, any contaminating organisms present in the solution may grow through the filter into the circulating fluid on the distal side. 3. In our opinion, the portal of entry for bacteria into the peritoneal cavity is more probably in and around the peritoneal tubes (especially the outflow tube) rather than in the inflow fluid itself. 4. It is further possible that organisms may enter the peritoneal cavity in a retrograde manner from the nonsterile suction system.

Many different types of tubes have been employed as peritoneal tubes. Rubber catheters or perforated small stainless

steel tubes have been frequently used as inlet tubes, whereas a large bore mushroom tip catheter or a stainless steel sump drain similar to the perforated suction tube used in operating rooms has been commonly employed as an outlet tube

Leakage of fluid around the peritoneal tubes, matting of the omentum and intestinal coils due to peritoneal irritation with resultant "channeling" and loss of fluid, and peritoneal infection are three immediate complications which

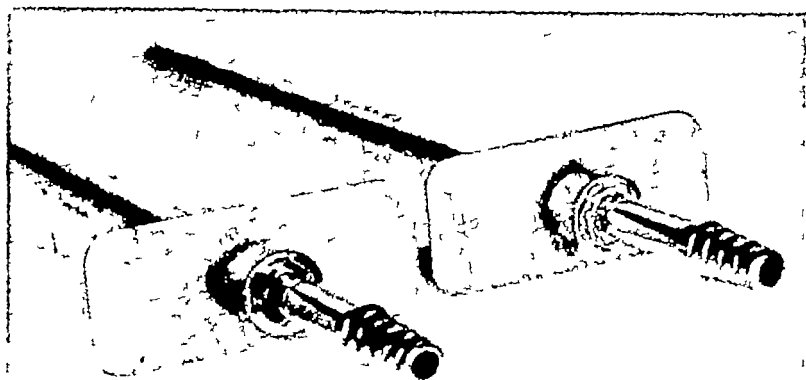


Fig 137 —Peritoneal tubes (sump drains) Note the malleable metal flanges which have been attached The drain on the right with airflow holes obliterated is used as the inflow tube

have prompted us to consider further modification of the tubes introduced into the peritoneal cavity Plugging of the tube has been reported frequently when rubber catheters have been used As shown in figure 137, we have employed identical modified stainless steel surgical suction tubes for both inflow and outflow, except that the air holes at the shoulder of the inflow tube have been obliterated, thereby rendering the inflow side a closed circuit This modification of the inflow tube makes it possible to reverse the direction of flow through the peritoneal cavity merely by interchanging the inner portions of the tubes, leaving the outer perforated sheaths in place. Such a reversal of flow may be necessary from time to time in order to avoid omental interference and "channeling"

Despite the foregoing modifications, we have continued to encounter difficulty with leakage of fluid around the tubes and also with peritoneal bacterial contamination We feel that leakage occurs because of relaxation of tissue of the

anterior abdominal wall around the tubes due partly to the fact that the rigid tubes must be introduced and fixed at an oblique angle, and partly to frequent movement of the tubes from respiration and movements of the patient. Peritoneal infection also may be introduced around the tubes as well as

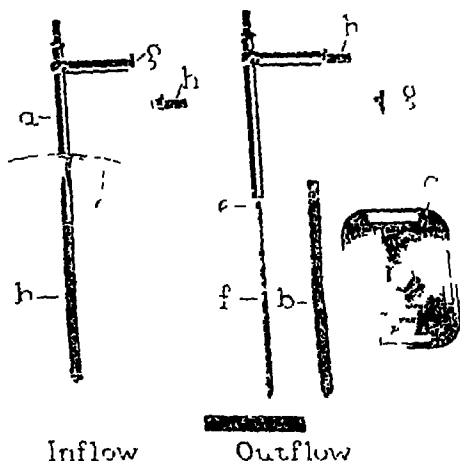


Fig. 138—Oppenheimer-Rosenak peritoneal tubes. The tube on the left (inflow) is assembled whereas the tube on the right (outflow) has been partly disassembled to show its component parts. Note difference in length of the intra-abdominal portions of the tubes (*b*). (By permission of C. D. Oppenheimer.)

through the air holes in the outflow tube, although meticulous care has been taken to keep the peritoneal tubes and the area surrounding them as nearly aseptic as possible.

Recently Oppenheimer and Rosenak have devised a new modification which may remedy some of the foregoing difficulties (fig. 138). Made of stainless steel the tube provides a rigid extra-abdominal portion (*a*) and a flexible intra-abdominal portion (*b*). This enables the tube to be introduced in a plane perpendicular to that of the anterior abdominal wall, which will allow tighter approximation of tissue edges around

the tube, as well as reducing motion of the tube with respiration to a minimum. The malleable metal flange (*c*) is adjustable with a screw (*d*), to allow for variations in thickness of the anterior abdominal wall. It then can be anchored with silk sutures to the skin of the anterior abdominal wall and sealed down either with collodion or with waterproof adhesive tape after the tubes have been placed. The intra-abdominal portion of the tube is made of tightly coiled stainless steel spring wire with a rounded tip (*b*). This will allow for easier introduction and placing of the tubes, and should reduce peritoneal inflammation from constant friction of a rigid tube rubbing against delicate peritoneal surfaces. The inner cores of the tubes are of stainless steel in the extra-abdominal portion (*e*) and of flexible rubber catheter in the intra-abdominal portion (*f*). The tubes are identical except for the length of the flexible intra-abdominal portion, the shorter being designed as inflow tube and the longer as outlet tube. Reversal of the direction of flow can be accomplished by interchanging the inner portions of the tubes, closing the side arm on the inflow tube with a metal plug (*g*) and inserting an adapter in the side arm of the outflow tube. On this adapter (*h*) is attached a rubber tube leading to a sterile glass funnel covered with sterile gauze to act as an air filter. Such an arrangement further reduces the possibility of introducing infecting organisms through the air inlet on the outflow tube. We have not as yet had an opportunity to use these tubes, but we are hopeful that they may aid in reducing the incidence of leakage and peritoneal infection.

The Procedure —*Prelavage Period* — Since, in a large number of cases of acute anuria and renal insufficiency on the basis of a reversible renal lesion, adequate renal function may be resumed spontaneously and since peritoneal lavage is not without numerous hazards, it should be withheld until clinical evidence of uremia appears or until it seems certain that spontaneous resumption of formation of urine will not occur. The optimal time for the institution of peritoneal lavage cannot be definitely stated, for it will vary with different patients. Constant clinical evaluation of the patient's condition, signs of progressive azotemia, failure of routine conservative meas-

ures to induce formation of urine, and weighing of the risks involved are the factors which must determine the optimal time for initiating the procedure

It has been our practice when it is decided to initiate peritoneal lavage, to make certain laboratory determinations before the procedure is undertaken. As a rule, a fairly complete chemical analysis of the patient's blood is obtained, in order that we may have accurate information as to the electrolyte balance of the patient's blood as well as the values of other crystalloid substances in the blood. In addition, concentration of hemoglobin, erythrocyte and leukocyte counts, sedimentation rate, hematocrit reading, plasma protein level, blood grouping (including the Rh factor), and coagulation time are determined. In some instances it is not possible to make so complete and detailed an analysis and when such is the case, the following studies should be sufficient: concentration of hemoglobin, leukocyte count, blood urea or nonprotein nitrogen, plasma chlorides, carbon dioxide combining power, plasma proteins, hematocrit reading, blood grouping, and coagulation time.

Lavage Period—The tubes are inserted with the patient under local or regional block anesthesia and with aseptic technique, through small incisions in the anterior abdominal wall, the inflow tube in the left upper quadrant of the abdomen, the outflow tube in the right lower quadrant. The inflow tube is directed toward the diaphragm, the outflow tube toward the cul-de sac. The incisions are then closed as snugly as possible around the tubes and covered with sterile dressings. Placing of the tubes in this way allows maximal peritoneal surface for dialysis. The procedure may be carried out with the patient in bed but it is better to do it in the operating room if the patient's condition permits his being moved. On completion of the operation the patient is returned to bed in a semi Fowler position, to facilitate perfusion of fluid over the peritoneal surface into the cul-de sac, which serves as a reservoir from which the fluid is removed by suction. Although the patient experiences little or no discomfort from the procedure $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.01 to 0.016 gm) of morphine sulfate or 1 grain (0.065 gm) of codeine sulfate

is administered for relief of any distress he might have. The rubber tubing, previously sterilized, is connected to perito-

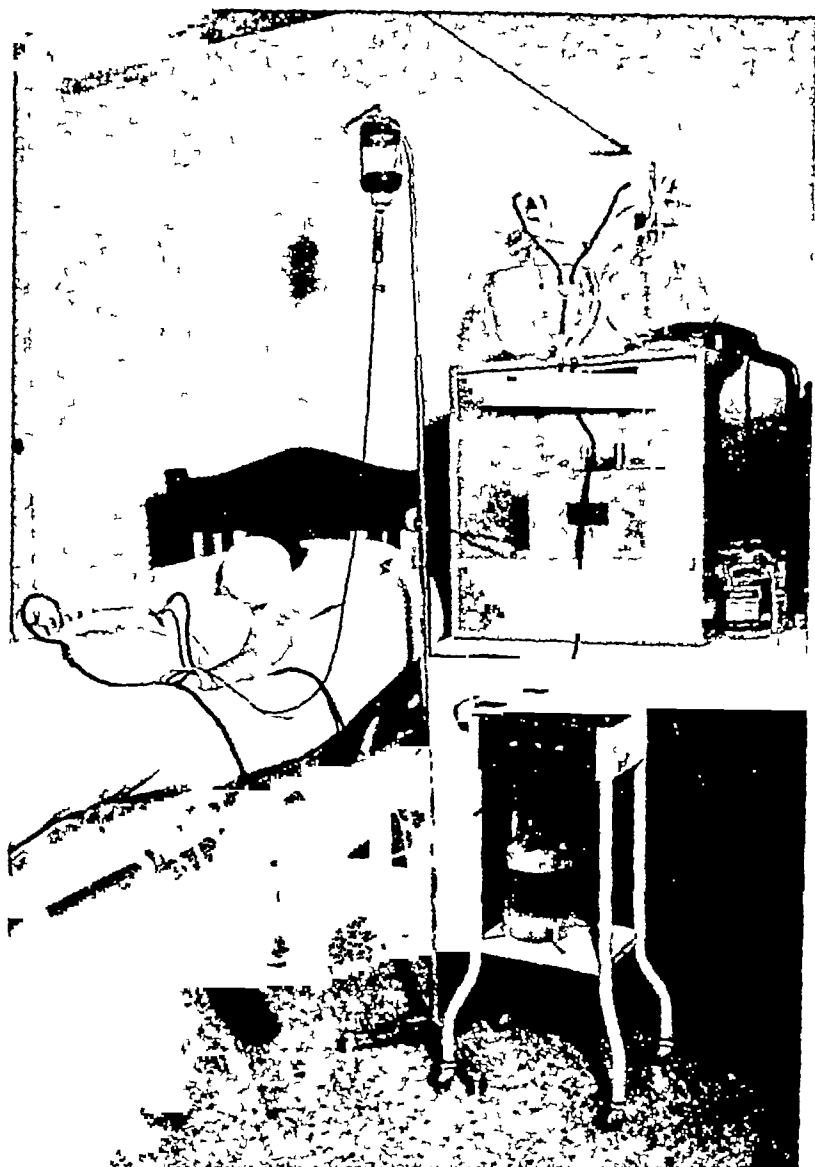


Fig. 139 —Apparatus for peritoneal lavage in use

neal tubes, suction, glass coil in water bath, drip bulb, and balloon flasks, technic as nearly aseptic as possible being used. Siphonage from the balloon flasks is established with a 50 cc sterile syringe. The flasks are connected in pairs, although

only one is used at any one time, in order that the flow may not be interrupted during the process of replacing empty flasks (fig 139)

Stopcocks are adjusted to allow as rapid a rate of flow as possible without causing discomfort to the patient. Seligman, Frank and Fine demonstrated in their animals that the optimal rate of flow for maximal clearance of urea across the peritoneum was 30 to 50 cc per minute (1,800 to 3,000 cc per hour). Kolff⁴⁰ expressed the opinion that the optimal rate of flow clinically is 16 to 20 cc per minute (1,000 to 1,200 cc per hour). Our experience has confirmed the first observation of Seligman, Frank and Fine that the removal of urea across the peritoneum is proportional to the rate of flow (figs 140 and 141), but thus far it has been impossible for us to accomplish the optimal rate of flow as suggested by them for our patients have complained bitterly of abdominal pain and nausea if the rate of flow was increased to more than 20 cc per minute (1,200 cc per hour). With a rate of flow less than 20 cc per minute, our patients have not complained of any discomfort. As soon as the flow of solution into the peritoneal cavity is established, continuous suction should be started although there is usually a lapse of time of twenty to thirty minutes before irrigation fluid appears in the suction bottle. It should be emphasized at this point that, if for any reason in the course of the lavage period it become necessary to discontinue the flow temporarily, the flow of fluid into the peritoneal cavity should be stopped before suction is turned off. Otherwise, it is possible to overdilend the abdomen with fluid, with resultant discomfort to the patient and leakage of fluid around the peritoneal tubes.

During the lavage period it is extremely important to watch the electrolyte balance of the patient's blood carefully. We have run a daily determination of the level of urea in the patient's blood, plasma chloride value, and carbon dioxide combining power. If the lavage fluid is electrolytically correct, the electrolytes in the blood should maintain themselves at normal or near normal levels without parenteral replacement. The value of the hemoglobin and erythrocyte count should be watched carefully at intervals of two or three days, for if a

significant fall of these values occurs, transfusion with whole blood may be indicated. Such transfusions should be given

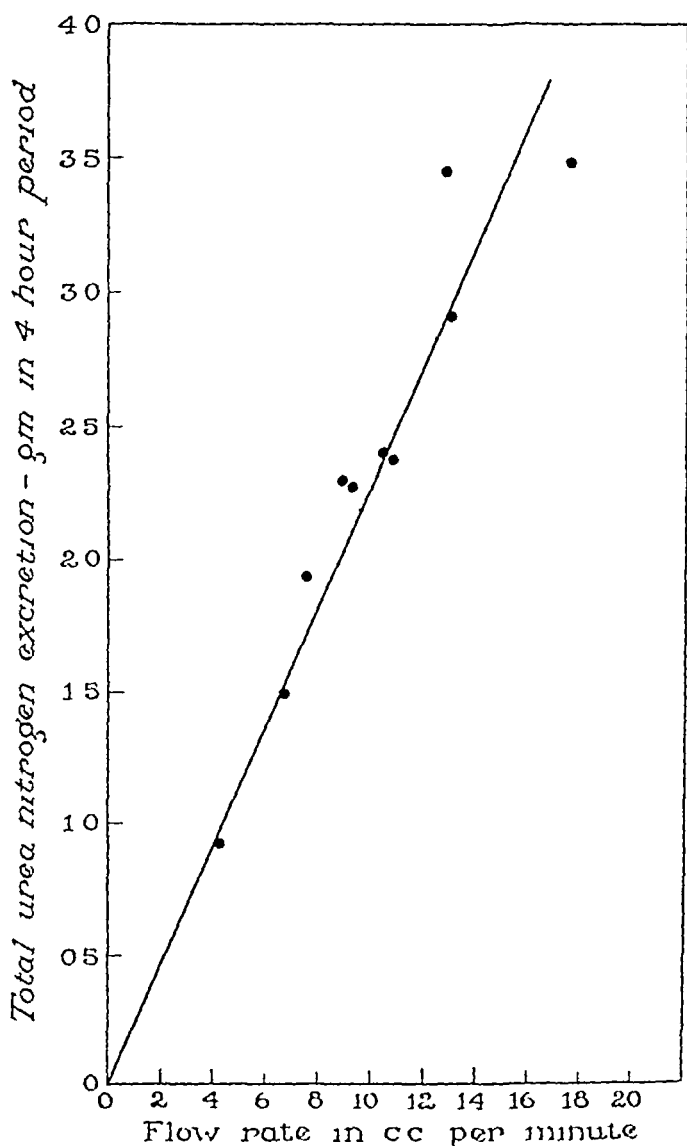


Fig. 110 (Case 1) —The relation of total urea nitrogen excretion to the rate of flow of fluid through the peritoneal cavity

only after the patient's blood has been grouped, and the patient's serum cross-matched with the donor's cells, in order to reduce to a minimum the possibility of further damage to the kidneys from a transfusion reaction. We have determined

the coagulation time of the patient's blood daily during the lavage period in order to assure ourselves that heparin was not being absorbed from the peritoneal cavity in amounts sufficient to affect the coagulability of the patient's blood. Determinations of the hematocrit reading, the level of the

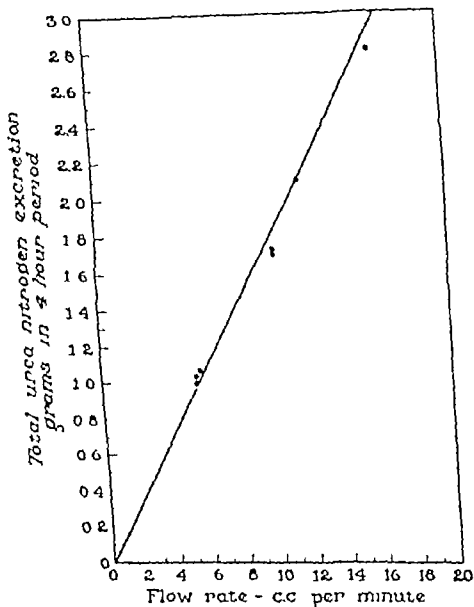


Fig 111 (Case 2) —The relation of total urea nitrogen excretion to the rate of flow of fluid through the peritoneal cavity

total plasma proteins and the erythrocyte count are valuable in estimating the state of hydration of the patient. Sudden rise of erythrocyte count together with an elevated hematocrit reading and high plasma proteins, is indicative of hemoconcentration and dehydration, whereas a rather sudden fall of erythrocyte count decreased hematocrit reading and a fall of the value for plasma proteins indicate hydremia, hemodilution and overhydration.

We have installed indwelling catheters in our patients during the period of anuria or oliguria and through the lavage period. When this is done, the urgency of which some such patients complain and the exertion and strain of attempting to use a bedpan or a urinal are eliminated. In addition, we have been able to measure accurately the urinary output, however small, and to recover all specimens for analysis of nitrogen, chloride and protein excreted.

Antibiotic Therapy—In regard to antibiotic therapy as prophylaxis against peritoneal infection, in addition to penicillin in the perfusion fluid, we have given our patients penicillin intramuscularly in a dosage of 30,000 units every three hours. In addition, in cases 3 and 4, we have also given 120,000 units of streptomycin intramuscularly every three hours. There is some question as to the advisability of using streptomycin parenterally in the presence of severe renal damage, with impaired excretion of the drug. However, we have never exceeded in dosage 1 gm daily, and have been constantly alert to signs of streptomycin toxicity. Thus far, we have felt that the risk of toxicity and further renal damage is less with streptomycin than with the use of sulfonamide compounds.

Parenteral Therapy.—Supplemental parenteral therapy is needed in most cases during the lavage period to maintain water balance, to supply vitamin balance, to maintain nutrition, and to correct anemia and hypoproteinemia. If the electrolyte content and osmolar concentration of the lavaging fluid are correct, then it should not be necessary to supply electrolyte substances such as chloride and bicarbonate by parenteral administration. However, only by close daily supervision of these values in the patient's blood can one be certain that supplementary quantities of these substances are or are not needed. Fairly frequently nausea and vomiting are complicating factors and may result in rapid depletion of the plasma chlorides, in which case intravenous injections of physiologic saline solution (0.9 per cent) may be indicated.

In the presence of acute urinary suppression, the temptation is great to administer increased volumes of fluid parenterally in an attempt to "force" the renal block. Such a

practice, however, is hazardous and frequently leads to overhydration with the development of peripheral edema or severe pulmonary edema. Adequate fluid must be provided to make up for that lost by vomiting, diarrhea, increased sweating, temperature elevation if present, and respiration, but the administration of amounts in excess of that needed to insure adequate fluid balance and to take care of the patient's fluid requirement should be avoided. As a general rule unless the patient has an extremely high temperature, or is losing copious amounts of fluid through abnormal channels, 1,500 to 2,000 cc daily should be adequate.

Dextrose in 5 per cent solution in distilled water is the solution of choice to supply both necessary fluid and nutrition to the patient. We have reinforced all parenteral dextrose solutions with vitamins B and C in amounts sufficient to prevent vitamin deficiency. Care should be taken not to administer hypertonic solutions intravenously during the lavage period. To do so may increase the tonicity of the blood sufficiently to cause absorption of fluid from the peritoneal cavity into the circulating blood with rapid hydremia and pulmonary edema.

If anemia becomes a factor for consideration, transfusion should be contemplated as mentioned previously, only after careful blood grouping of the patient's blood and cross-matching with the donor's cells. It is a well established fact that patients who have severe renal insufficiency and uremia respond poorly to transfusion, are prone to develop reactions, and not infrequently develop acute pulmonary edema. The exact explanation for this tendency is not entirely clear although several hypotheses have been advanced. However it is of the utmost importance to bear this in mind if the need for transfusion arises. As a rule such a patient will tolerate small daily transfusions of 150 to 175 cc without incident, whereas a single transfusion of 500 cc may invite disastrous results.

If the level of plasma proteins tends to decrease and significant hypoproteinemia appears imminent protein replacement therapy in the form of whole blood, or albumin, or one of the hydrolyzed proteins is indicated.

indicated Any such substance should be used with caution and its volume should be included in the total for daily parenteral fluid intake

Whether or not the patient should be allowed to eat or take fluids by mouth during the lavage period is somewhat of a debatable point Whether dialysis proceeds more satisfactorily if the bowel is kept at rest, or whether it is enhanced by moderate intestinal activity cannot be stated without further study In our experience, in the presence of renal failure and uremia, anorexia, nausea and vomiting are the rule and it is necessary to rely entirely on parenteral administration for maintenance of fluid and nutritional balance We, therefore, have preferred to withhold all fluids and food by mouth during the lavage period

During the early days of the lavage period, symptoms and signs characteristic of typical or true uremia may be present, and must be handled accordingly It may be necessary to rely heavily on sedatives if the patient is restless or appears to have pain, soothing lotions may be needed for pruritus, which frequently accompanies uremia, and, if nausea and vomiting persist, or if signs of paralytic ileus develop, passage of a gastric tube for gastric lavage or of a Miller-Abbott tube for intestinal decompression may be indicated However, if the procedure progresses satisfactorily, within three or four days marked subjective and objective improvement may be observed with alleviation of these distressing symptoms

At the termination of the lavage period, it is advisable to stop the inflow of fluid and to continue suction until the greater portion of fluid remaining in the peritoneal cavity has been removed The peritoneal tubes are then loosened and removed and the small incisions are covered with sterile dry dressings Spontaneous healing occurs within four or five days after the tubes have been removed and by the time the patient's general condition allows him to become ambulatory Frequently, the question has arisen as to the optimal duration of the lavage period Kolff⁴⁰ has expressed the opinion that to employ peritoneal lavage for longer than thirty-six hours is to increase the hazard of peritonitis greatly We, however, are of the opinion that if peritoneal infection can be prevented

or, if it occurs, can be kept under control, continuous irrigation should be maintained until the level of urea in the blood falls to less than 100 mg per 100 cc, until the twenty-four hour excretion of urine exceeds 1,000 cc in volume, or until the amount of urea excreted in the urine equals or exceeds the amount excreted in the dialysate in the corresponding twenty-four hour period.

REPORT OF CASES

We have employed peritoneal lavage in 4 cases of acute renal failure with anuria and uremia. In 2 of these cases the treatment was successful, with ultimate recovery, and in 2 it was unsuccessful.

CASE 1—This case has been reported in detail elsewhere.¹⁷ A summary of the pertinent data follows.

Prelavage Period—The patient, a man 49 years of age, was admitted to the Clinic and immediately hospitalized. He complained of headache, nausea, vomiting, jaundice, and oliguria of seven days duration. His history revealed that he had partaken of moderate amounts of alcohol (4 to 8 fluidounces [120 to 240 cc] daily) for some time previously. In his work as an electrician he had found carbon tetrachloride to be an excellent grease solvent as well as a dryer. Ten days before admission he had used a quantity of the compound to clean grease from a pair of trousers and during the morning of the eighth day before admission he had used 1 gallon (1 liters) of pure carbon tetrachloride in cleaning fresh paint from the staircase of his home. Exposure time to the fumes during this procedure was estimated to be approximately two hours in a closed house. Working on his knees brought him into sufficiently close proximity to the cleaning fluid to expose him to the fumes in lethal concentration. He took two drinks (1 fluidounce [120 cc.]) of whisky prior to his evening meal and noted some anorexia at that time. During the night he was awakened with nausea and vomited several times. A severe chill then developed which lasted several minutes.

The following morning the patient experienced extreme weakness and fatigue with recurrence of nausea and vomiting. During the latter part of the morning, twenty hours after exposure, he voided the last known sizable quantity of dark brown urine. He did not call a physician until thirty-six hours later when severe dull aching pain developed in the right upper quadrant of the abdomen. On examination he was found to be jaundiced, his liver was enlarged, and he was thought to be in shock. He was hospitalized and given

fluids and large doses of vitamins intravenously. Albuminuria, oliguria, nausea, vomiting and jaundice persisted and the patient was transferred by ambulance to the Clinic on the eighth day after exposure. Prior to transfer, the daily excretion of urine averaged 50 cc. The urine was brownish red and gave a 4 plus reaction for albumin.

On admission to the Clinic the patient was rational and oriented. He had a temperature of 98.2° F, a pulse rate of 80 beats per minute, and blood pressure of 138 mm of mercury systolic and 80 diastolic. Jaundice was graded 2 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) over the entire body and sclerae, and subconjunctival hemorrhages were noted in both eyes. Edema, graded 1, of the face and lower extremities was present. The liver was tender and palpable 3 cm below the right costal margin. There was questionable ascites. The patient was catheterized and 15 cc of urine were obtained, revealing a specific gravity of 1.014, albumin graded 3 (on the basis of 1 to 4) and erythrocytes graded 1 (on the basis of 1 to 5). Urine culture was negative. The content of hemoglobin was 12.6 gm per 100 cc of blood and the leukocyte count was 8,400 per cubic millimeter of blood. Prothrombin time was 23 seconds (normal 17 to 19 seconds). The value for cholesterol esters was 27 mg per 100 cc of plasma, and that for bilirubin was 11.6 mg per 100 cc of serum, with a direct reaction. Other laboratory data are detailed in table 6.

Management of the patient's hepatic insufficiency consisted in daily intravenous administration of hydrolyzed protein, glucose and vitamin supplements including nicotinamide, hykinone and cevalin. Attempts were made to combat acidosis by the administration of sodium bicarbonate in 5 per cent solution. Conservative measures, such as intravenous administration of aminophylline in doses of 3¾ grains (0.24 gm) twice daily and continuous application of hot packs to the flanks were employed in the hope of increasing excretion of urine and improving renal function. During the second day in the hospital unsuccessful attempts were made to pass a multiluminal tube into the duodenum with the ultimate hope of utilizing the mucosal surface of the upper part of the small intestine as a dialyzing membrane.

Lavage Period—On the third day in the hospital it was decided to attempt peritoneal lavage. This was the ninth day of oliguria and the tenth day after exposure to carbon tetrachloride. During this time attempts made to meet the patient's fluid requirements and to balance the blood electrolytes by parenteral means had been only partially successful. Lavage was instituted according to the technic described previously, modified mammalian Tyrode's solution being used as the perfusing fluid. Penicillin in a concentra-

TABLE 6
CHEMICAL COMPOSITION OF BLOOD IN CASE 1

	Day	Urea mg per 100 cc. of blood	Creati- nine mg per 100 cc of blood	Protein gm per 100 cc of serum	Chole- sterol mg per 100 cc of plasma	Milliequivalents per liter*						Calcium (serum)	Phos- phate (serum)
						Sulfate (serum)	Chloride (plasma)	HCO ₃ ⁻ (CO ₂ Combining Power) (plasma)	Sodium (serum)	Potas- sium (serum)			
Pre lavage period	1	211		6.1	103	8.5	82.9	16.3					
	2	211					83.9	19.7					
	3	216					81.9	21.1		4.5			
	4	208		6.0			99.5	16.8	145.2	5.0			
	5	194		6.3	75		98.8	23.1					
	6	190	11.7	5.8	68		101.5	17.6	138.3	5.7		3.5	5.6
	7	176		5.6		5.1	101.5	20.6					
	8	158	12.5	6.1	105	4.6	111.9	18.9	147.0	1.6		3.9	3.5
	9	182		6.8			102.2	21.0					
	10	224			109		101.5	25.0	119.6	5.2			
Average period													

* For normal milliequivalent values of blood plasma, consult figure 134

tion of 5,000 units per liter and 0.25 mg of heparin per liter were added.

The first forty-eight hours of the lavage period were without incident and the patient exhibited marked subjective improvement. He felt better generally, nausea disappeared and he was able to retain fluids taken by mouth. Physical examination revealed the lungs to be clear, and the degree of peripheral edema noted on admission had not increased.

On the following day (sixth day in the hospital) the patient became mildly irrational, exhibited a pulse rate of 100 beats per minute and a rise of temperature to 101° F. There was a moderate but definite increase of peripheral edema. Moist rales were heard in the base of the right lung and a roentgenogram of the thorax revealed findings suggestive of beginning bronchopneumonia. Leukocytes numbered 27,900 per cubic millimeter of blood. Ninety cubic centimeters of urine obtained by catheterization on this day revealed a specific gravity of 1.007, albumin graded 3, erythrocytes graded 2, and pus cells graded 1. Culture from peritoneal washings was positive for *Aerobacter aerogenes*, *Pseudomonas* and *Micrococcus*.

Penicillin, which had been administered in the dosage of 30,000 units intramuscularly every three hours since initiation of lavage therapy, was increased to 50,000 units every three hours, and penicillin in the lavage fluid was increased from 5,000 units per liter to 10,000 units per liter. Signs of progressive hepatic insufficiency were noted as the total cholesterol level decreased from 103 mg per 100 cc of plasma (normal 150 to 250 mg per 100 cc) on admission to 68 mg per 100 cc, with cholesterol esters of 27 to 28 mg per 100 cc of plasma (normal 100 to 175 mg per 100 cc) (table 6). Depleted plasma proteins, probably due largely to failure of synthesis of protein in the presence of severe hepatic damage but possibly in part due to loss of protein across the peritoneum, were replenished by repeated intravenous administration of protein hydrolysate, plasma and whole blood. Hypocalcemia, first noted on the fifth day in the hospital, was treated with calcium gluconate given intravenously. The blood pressure rose to 176 mm of mercury systolic and 100 diastolic on the seventh day in the hospital. The general condition of the patient remained about the same. However, during the next two days, the patient's course was progressively downhill with increasing symptoms and signs of exhaustion, bronchopneumonia, pulmonary edema and deepening coma. He died on the tenth day after admission.

Necropsy Findings—Necropsy revealed deep jaundice and a moderate amount of edema in the subcutaneous tissues. The peritoneal cavity contained 1,500 cc of yellowish pink fluid (irri-

gation fluid) The parietal peritoneum and intestinal coils showed multiple areas of injection with small subserosal hemorrhages, and patches of fibrinopurulent exudate. The lower lobes of both lungs revealed a patchy increase of consistency and the cut surface disclosed a moderate degree of edema and frothing. Pus could be expressed from the small bronchi of both lower lobes. The liver was enlarged and was yellowish green. On cut surface, the markings were distinct. There was moderately severe submucous edema of the entire gastro-intestinal tract. The kidneys were large and red and were normal in consistency. The cut surface showed normal markings except for swelling of the cortex. Examination of the brain showed only mild edema.

Histologic examination of the liver revealed intact lobular architecture with evidence of cellular regeneration. Many of the bile canaliculi were obstructed by bile thrombi. The hepatic cells in the central portions of the lobule contained increased amounts of bile pigment and had undergone mild infiltration with fat. In sections of the kidneys the tubules were flattened. Mitotic figures were numerous among the epithelial cells and it was apparent that extensive regeneration had occurred. A few of the tubules contained desquamated epithelial cells and occasional groups of polymorphonuclear cells. In sections cut from the lower lobes of the lungs the alveoli were filled with serum and polymorphonuclear leukocytes. Aside from exudate on the serosa of the jejunum and the capsule of the spleen sections of other organs did not reveal anything remarkable.

The anatomic diagnoses in this case were (1) toxic hepatitis due to carbon tetrachloride with hypertrophy and regeneration of the liver, (2) toxic degeneration of the renal tubules, with regeneration, (3) peritonitis, (4) pulmonary edema with bronchopneumonia and (5) edema of the brain.

Comment—Although there was anatomic evidence of both peritonitis and bronchopneumonia we are of the opinion that the immediate cause of death in this case was pulmonary edema with circulatory failure and increasing uremia. Bronchopneumonia probably developed as a terminal event and peritonitis undoubtedly was a contributory factor, in that formation of peritoneal exudate reduces the efficiency of the filtering surface in addition to 'channeling' which reduces the area of peritoneum available for dialysis. This is suggested by the fact that during the first five days of dialysis there was a sharp decrease of the urea level in the blood (table 6) with large amounts of urea recovered in the peritoneal fluid.

TABLE 7
UREA EXCRETION VIA PERITONEUM AND KIDNEYS IN CASE 1

	Day	Blood Urea, mg per 100 cc	Dialysate			Urine		
			Outflow, cc in 24 hr	Total Urea, gm	Urea, mg per 100 cc	Output, cc	Total Urea, gm	Urea, mg per 100 cc
Pre-lavage period	1	234						
	2	214						
Lavage period	3*	216	10,050	22.7	225.9	25		
	4	208	14,100	27.6	195.7	50		
	5	194	10,100	20.1	199.0	10		
	6	190	11,000	18.6	169.1	90	0.56	623.3
	7	176	14,200	21.0	147.7	110	0.76	686.3
	8	158	7,350	10.5	112.9	110	0.75	677.3
	9	182	16,300	15.1	94.5	105	0.85	804.8
	10†	221	9,650	7.3	75.6	20		
	Total		92,750	143.2		520	2.92	

* Determinations on dialysate based on twelve hour total only

† Determinations on dialysate based on sixteen hour total only

(table 7), whereas during the last three days of life, excretion of urea across the peritoneum decreased markedly, with resultant increase of urea concentration in the blood (table 7 and fig 142) One might further speculate that increased catabolism of endogenous protein incident to terminal infection and increased body temperature might result in increased

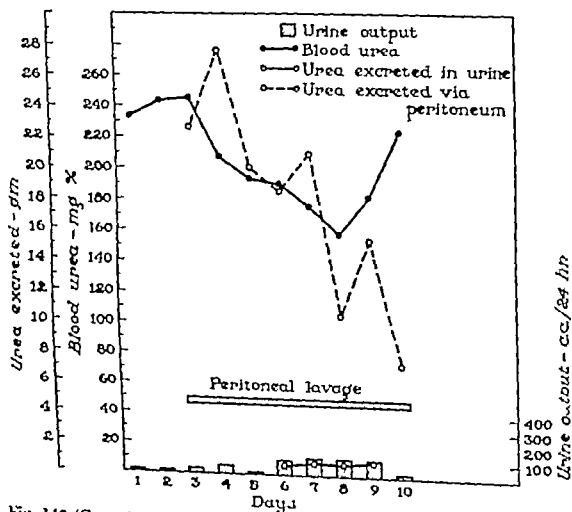


Fig 112 (Case 1) —Course of azotemia, daily urea excretion via the kidneys and the peritoneum and daily urine volume.

production of nitrogenous waste products which the patient was unable to eliminate either renally or extrarenally.

In this case, as in our other cases, there is a marked disproportion between the blood urea levels and the total quantity of urea removed by dialysis due to the fact that during lavage urea is removed not only from the blood but also from urea stores in cells and fluid of all the tissues in the body.

That the irrigating solution we were using was not physiologic and required further adjustment of composition in order to maintain normal electrolyte balance in the blood was illus-

trated to us by this case Retrograde absorption of chloride from the peritoneal cavity into the blood plasma was suggested by the fact that within twenty-four hours after lavage

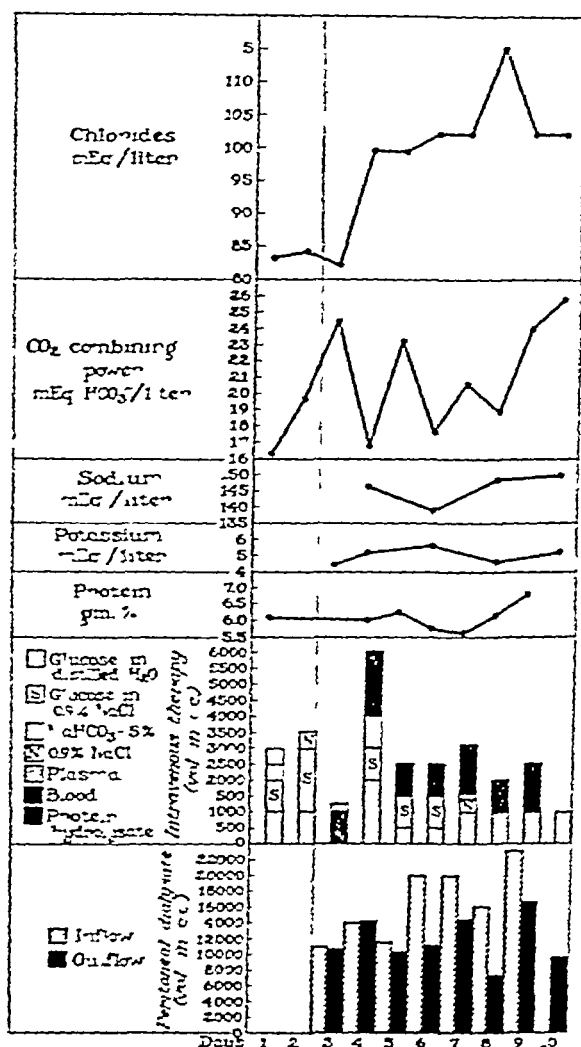


Fig 143 (Case 1) —Trend of the various constituents of the blood showing effects of parenteral administration of different fluids on daily electrolyte balance

was instituted the plasma chloride concentration increased from a subnormal to a normal level even though the patient had not received any chloride parenterally (fig 143) On the fifth day of dialysis plasma chlorides soared to a level of 114.9 milliequivalents per liter with a corresponding decrease

TABLE 8
APPROXIMATE FLUID BALANCE (Cc IN 24 Hr) IN CASE 1

Pre-lavage period	Day	Intake										Dialysate		Output	
		Oral	Intravenous								Total	Inflow	Out-flow		
			Dextrose in Distilled H ₂ O		Dextrose in 0.9% NaCl		0.9% NaCl	NaHCO ₃ 5%	Plasma	Whole Blood					Protein Hydrolysate
			10%	5%	10%	5%									
Lavage period	1		1,000		1,000	500	500				3,000		15		
	2		1,000		1,000	500					3,500		15		
	3						250			1,000	1,250	10,050	25		
	4		2,000		1,000		1,000			2,000	6,000	14,100	50		
	5	380	500		1,000					1,000	2,880	10,100	10		
	6	135	500		1,000					1,000	2,635	20,000	90		
	7	30	1,000			300		250	500	1,000	3,080	20,000	110		
	8	120						1,000		1,000	2,120	16,000	7,350	110	
	9	50	1,000							500	1,000	2,550	23,000	16,300	105
	10		1,000									1,000		9,650	20
Total		2,000	6,000	1,000	5,000	1,300	1,750	1,250	1,000	8,000	28,015	115,500	92,750	550	

Total intake 143,515 cc
Total output 93,300 cc

edema, and peritonitis not developed to damage the delicate dialyzing membrane, the patient might have recovered, for although there was unmistakable evidence of widespread hepatic and renal damage, anatomic regeneration had progressed to a point at which regeneration of function might have been expected within a short time

CASE 2 —Prelavage Period —The patient, a 73 year old man, was admitted to the Clinic, complaining of urinary difficulty of ten years duration. He had noticed gradual decrease of the caliber of the urinary stream during this period, and on two occasions two years and two months, respectively before admission, had experienced acute retention necessitating catheterization. Diuria, nocturia and hesitancy were also present

Physical examination revealed a small, well preserved, elderly man, weighing 116 pounds (52.6 kg). Blood pressure was 136 mm of mercury systolic and 74 mm diastolic. The pulse rate was 72 beats per minute and the temperature 98.2° F. The lungs were clear and examination of the heart did not reveal significant abnormalities. The edge of the liver was palpable at the right costal margin on deep inspiration and a large right indirect inguinal hernia was demonstrated. Rectal examination revealed a hypertrophied prostate (graded 3 on the basis of 1 to 4) which was firm in consistency and nontender. There was no peripheral edema.

Routine urinalysis revealed a specific gravity of 1.019 and was otherwise negative except for 30 pus cells per high dry field. The concentration of hemoglobin was 15.6 gm per 100 cc. of blood (103 per cent). Erythrocytes numbered 4,890,000 and leukocytes 5,500 per cubic millimeter of blood. The sedimentation rate was 6 mm in one hour (Westergren method). A roentgenogram of the thorax revealed torsion of the aorta and some increase of bronchovesicular markings at the right cardiophrenic angle. A roentgenogram of the kidneys, ureters and bladder did not reveal any significant abnormalities. The blood urea was 21 mg per 100 cc. The patient's blood group was A and he was Rh positive. Culture of the bladder urine was found to be positive for *Streptococcus faecalis* and there were 160 cc. residual urine in the bladder.

Diagnosis was made of prostatic hypertrophy with urinary obstruction and right inguinal hernia, and transurethral prostatic resection was advised. The patient was admitted to the hospital four days after admission to the Clinic and the following day while he was under spinal anesthesia, cystoscopic examination followed by transurethral prostatic resection was done, a total of 72 gm of adenofibromatous hyperplastic tissue being removed.

Bleeding presented more than usual difficulty to the procedure, but was adequately controlled by a pear-shaped bag catheter inserted and inflated to 40 cc at the conclusion of the operation. During the operation a transfusion of 500 cc of citrated whole blood was given from a type O, Rh positive donor.

Although the patient withstood the operation satisfactorily, oliguria developed the second day following, with a twenty-four hour urinary output of only 350 cc. Blood urea was found to be

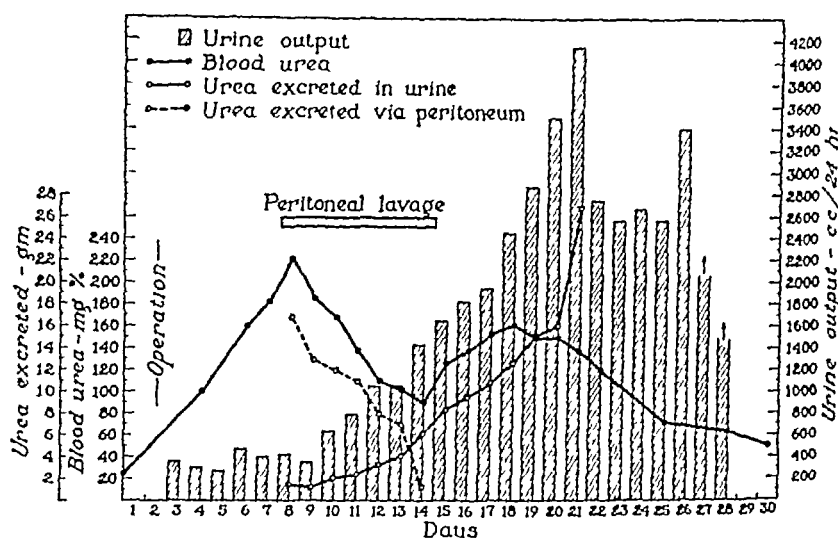


Fig 144 (Case 2) —Course of azotemia, daily urea excretion via the kidneys and the peritoneum, and daily urine volume. The last observation on blood urea was on the thirty-fourth day after admission.

100 mg per 100 cc, plasma chlorides 76.1 milliequivalents per liter and carbon dioxide combining power 19.8 milliequivalents of HCO_3^- per liter. The concentration of hemoglobin was 11.5 gm per 100 cc of blood (77 per cent). Erythrocytes numbered 3,800,000 and leukocytes 15,100 per cubic millimeter of blood. Routine urinalysis revealed a specific gravity of 1.015, albumin graded 4, erythrocytes graded 5 and pus cells graded 4. Routine measures, consisting of parenteral fluid therapy and hot packs to loins, were instituted. The following day, nausea, vomiting and marked abdominal distention developed, and a duodenal tube with continuous suction was instituted.

During the next four days, the twenty-four hour urine output averaged 275 to 300 cc, but the urea and creatinine levels mounted steadily (fig 144). The patient became disoriented and drowsy, with increased nausea and vomiting, and showed signs of gradual deterioration. Because of this, on the eighth day in the hospital (seven days after operation) it was decided to institute peritoneal lavage.

Lavage Period—At the time peritoneal lavage was started, the concentration of hemoglobin was 7.5 gm per 100 cc of blood (50 per cent) Erythrocytes numbered 3,080,000 and leukocytes 9,300 per cubic millimeter of blood Coagulation time was 10 minutes Pertinent laboratory data are detailed in table 9

The procedure followed was that described previously and the irrigation fluid used was "P" solution (table 5) with the addition of 10,000 units of penicillin and 1 mg of heparin per liter Because of the fact that an increased amount of heparin was added to the solution, daily determinations of the coagulation time were done for three days, but no increase was noted

Marked subjective and objective improvement was noted within twenty four hours Nausea and vomiting stopped and the patient's mental condition became more clear There was no evidence of myocardial failure, the lungs remained clear to physical examination, and peripheral edema did not develop Fluid requirements were met primarily by the use of dextrose in distilled water in 5 per cent solution fortified with vitamins B and C (table 10) In addition, the patient was given $7\frac{1}{2}$ grains (0.49 gm) of aminophylline daily intravenously

Partly because of continued bleeding from the prostatic bed, and partly because of his uremia, the patient exhibited a stubborn anemia for which repeated small blood transfusions were needed

On the fifth day of dialysis abdominal distention and a recurrence of nausea and vomiting developed and no peristaltic sounds were heard on auscultation of the abdomen These findings together with a leukocyte count of 22,400 per cubic millimeter of blood, elevated temperature, and the fact that *Escherichia coli* and *Aerobacter aerogenes* had been cultured from the peritoneal washings, led us to believe that peritonitis with paralytic ileus had developed Intramuscular dosage of penicillin was increased to 100,000 units every three hours A Miller Abbott tube with constant Wangenstein suction served to reduce the abdominal distention and within three days temperature and leukocyte count ~~returned~~

[illegible]

TABLE 10
APPROXIMATE FLUID BALANCE (Cc in 24 Hr) in Case 2

	Day	Intake							Dialysate		Output			
		Oral	Intravenous					Total						
			5% Dextrose in		10% Dex- trose	Plasma	Whole Blood							
			Distilled H ₂ O	0.9% NaCl										
Prelavage period	1							2,500						850
	2		2,000					3,200 ¹			350	500		1,175
	3	200	3,000					1,800			300	875		1,075
	4		1,800					1,500			275	800		1,075
	5		1,500					1,100			475	600		1,075
	6	100	1,000					1,500			100	700		1,100
	7		500	1,000										
Lavage period	8	25	1,000					1,025	12,600	11,140	150	500		950
	9	390	1,200					1,810	10,000	7,810	372	100		772
	10	150	1,500					2,200	13,600	10,750	644	450		1,094
	11	270	1,500					2,270	14,200	11,250	719	250		999
	12	310	1,000		1,000			2,310	14,900	10,395	1,008	275		1,283
	13	230	2,000					2,480	16,350	10,395	1,056	100		1,156
	14	250	2,000			500		2,750	5,000	2,518	1,412	625		2,037

TABLE 10—(Continued)

TABLE 10 — (Continued)													
Postoperative Period	Day	Intake						Dialysate		Output			
		Oral	Intravenous				Total	Inflow	Outflow	Urine	Emesis	Total	
			5% Dextrose in		10% Dex- trose	Plasma							Whole Blood
			Distilled H ₂ O	0.9% NaCl									
		435	2,000			500	250	2,935			1 650	100	1 750
	15	780	1 000	1 000			250	3 030			1 750		1 750
	16	1,375	2,000			500	250	3 625			1 953		1 953
	17	1 525	1 000					3 025			2,450		2,450
	18	1 920	1,500					3 420			2,875		2 875
	19	2,553		1 000				3 553			3 500		3,500
	20	2,600		1 000				3 600			4,150		4 150
	21	2,010	1 000					3 010			2,750		2 750
	22	3,080						3 080			2,575		2 575
	23	3,475						3 475			2,675		2 675
	24	2,570						2,570			2 575		2 575
	25	2 860					500	3 360			3 100		3 400
	26	2 975						2,975			2 030		2 030
	27	2 600						2,600			1 420		1 420
	28	33 013	20 500	4 000	1 000	2 000	2 250	70 763	86 650	64,258	43,214	6 475	49 719
	Total												

Total intake 157,113 cc.

Total output 113,977 cc.

Eight days after lavage had been discontinued, the patient was allowed out of bed. At this time, he began to manifest edema of his feet and ankles which, up to that time, had been absent. It was our impression that this was partly static edema appearing in dependent position of the body after three weeks in bed, and partly due to increased sodium and chloride intake with resultant increase of plasma sodium plus hypoproteinemia. Edema disappeared within five days and he was dismissed from the hospital on the twenty-eighth day after admission.

Comment—The exact cause for acute renal failure with oliguria and uremia in this case is not clear. The explanation most frequently advanced for such an occurrence after transurethral prostatic resection is that through dilated prostatic veins, exposed during operation, distilled water used to wash the denuded prostatic bed is absorbed, with resultant hemolysis of red cells and obstruction of the renal tubules of the "lower nephron" type. Although this may be the explanation for the postoperative urinary suppression in this patient, one wonders if, in this and similar cases, stimulation of the deep prostatic nerve plexus could produce a reflex type of anuria similar to that produced by Trueta and associates in animals.

The course of lavage in this patient was uneventful, except for the episode of what appeared to be paralytic ileus. However, if as we supposed, this was secondary to peritonitis, the infection resolved spontaneously with conservative treatment even though lavage was not interrupted.

As in the previous case, the concentration of urea in the urine exceeded that in the peritoneal fluid, even in the presence of severe, though temporary, renal damage (table 11).

Depleted plasma protein values were an important factor in this case. This could be explained in part by the patient's persistent anemia, but the presence of protein in the dialysate in sizable quantities lends support to the possibility that protein may be lost from the plasma across the peritoneum in significant amounts. Depletion to critical levels was avoided by transfusions of whole blood and plasma and the plasma protein level rose spontaneously after cessation of lavage and restoration of the patient's normal state of nutrition.

Our prediction and hope that "P" solution would be a satisfactory irrigating fluid from the standpoint of electrolyte

TABLE II
UREA EXCRETION VIA PERITONEUM AND KIDNEYS IN CASE 2

Day	Blood Urea mg per 100 cc.	Dialysate		Urine		
		Outflow cc in 24 hr	Total Urea gm	Urea mg per 100 cc	Output cc	Total Urea gm
Before nitrite ion						
1	24					
2	100					
3	160					
4	182					
5	182	11 110	16.1	147.1	150	1.5
6	182	10 710	12.9	161.8	372	1.2
7	182	11 280	11.9	111.3	611	2.0
8	182	10 103	11.1	98.1	719	2.1
9	182	10 084	8.2	79.2	1 008	3.3
10	182	11 110	7.1	68.5	1 056	1.2
11	182	11 110	1.7	19.7	1 112	0.2
12	182				1 650	8.1
13	182				1 750	9.0
14	182				1 933	10.8
15	182				2 350	12.7
16	182				2 815	18.0
17	182				3 103	16.0
18	182				1 100	20.0
19	182				1 112	100.1
20	182					
21	182					
22	182					
23	182					
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283	182					

balance was borne out by the fact that during the lavage period plasma electrolytes remained in normal balance. Three injections of 0.9 per cent sodium chloride solution were given during the postlavage period to combat a tendency to hypochloremia in the presence of increasing urinary excretion of chloride until the patient's oral intake of salt reached a satisfactory level for maintenance (fig. 145).

Of interest is the curve of the blood urea levels (fig. 144). At the time lavage was discontinued, the level of urea in the blood had decreased to 90 mg per 100 cc. However, in the next four days it rose gradually to 162 mg per 100 cc of blood despite daily increasing volume of urine. Then it again began to decrease to a level of 50 mg per 100 cc six days after the patient's dismissal from the hospital. This phenomenon has been observed in cases reported elsewhere, and is apparently due to the fact that, despite adequate volumes of urine excreted, the concentration of urea in the urine is not sufficiently high at the time lavage is discontinued to prevent a rather sudden secondary rise with gradual decrease as the concentration of urea in the urine increases.

As in our other cases, there was a discrepancy between the volume of fluid entering the peritoneum and that recovered amounting to about 22 liters (table 10). This difference over a period of seven days could be explained on the basis of loss of fluid by leakage around the peritoneal tubes, a complication with which we had considerable difficulty in this case.

CASE 3 —Prelavage Period —The patient, a woman 34 years of age, was admitted to the Clinic and immediately hospitalized.

Six days previously, we learned, she had been admitted for emergency treatment to a hospital elsewhere because of severe lower abdominal cramps accompanied by profuse vaginal bleeding. She had had two uneventful full-term pregnancies previously, and on admission to the hospital she had stated that her last normal menstrual period had occurred about twelve weeks before. She had not appeared acutely ill on admission and had been found to have a firm regular pulse rate of 100 beats per minute with a blood pressure of 110 mm of mercury systolic and 70 diastolic. The fundus uteri had been palpated behind the symphysis pubis and bleeding had been slight in amount. Bleeding, however, had continued, and after blood grouping and cross-matching had been done, the patient

had been taken to the operating room. At this time, the cervix uteri had been found to be 4 cm dilated with a large amount of tissue

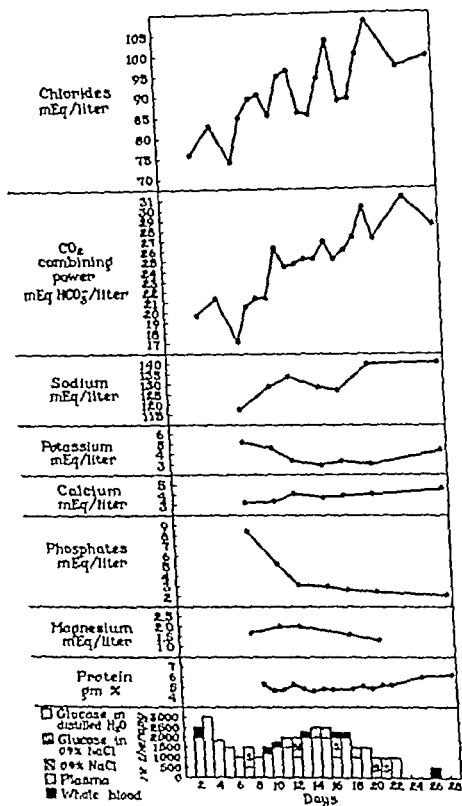


Fig 11a (Case 2) —Trend of the various constituents of the blood showing effects of parenteral administration of different fluids on daily electrolyte balance

presenting. The tissue had been removed intact with ovum forceps and the interior of the uterus had been explored. Bleeding had not subsided and the uterus had been packed with 2 inch (5 cm) plain gauze.

On the patient's return from the operating room, her color had been good and her pulse rate had been 120 beats per minute. A whole blood transfusion had been started, but after 125 cc had been received, she had had a severe chill and had become cyanotic, a weak rapid pulse had developed with a fall of blood pressure to 90 mm systolic and 75 mm diastolic. She had been placed in oxygen immediately and the foot of the bed had been elevated. After these measures cyanosis had disappeared although her pulse had stayed rapid and the blood pressure had stayed at low levels through the remainder of the day.

The following day, a catheterized specimen of dark brown urine had been obtained and found to contain a great deal of blood, as determined by microscopic and chemical examination. A diagnosis had been made of hemolytic transfusion reaction. The patient's general condition had appeared satisfactory although she had a rapid pulse of good quality.

Study of the patient's and donor's blood had revealed, we were informed, that the patient, who was type O, had inadvertently received type A blood.

On the second day the vaginal pack had been removed with no recurrence of bleeding. The patient had received 1,200 cc of fluid by mouth and had excreted 500 cc of dark brown urine, which microscopically showed albumin graded 4, and erythrocytes graded 4. The concentration of hemoglobin had been 7.5 gm per 100 cc of blood with 3,690,000 erythrocytes and 14,550 leukocytes per cubic millimeter of blood.

The following day the patient had been subjectively much improved except for some ringing in the ears. She had taken 2,510 cc of fluid by mouth and had been given 2,000 cc of sixth-molar sodium lactate in 5 per cent dextrose solution, plus 500 cc of 5 per cent dextrose in 0.9 per cent sodium chloride solution intravenously. Urinary output for this day had been 350 cc.

On the fourth day nausea, epigastric pain and moderate facial edema had developed. Intake of fluid for this day had consisted of 1,800 cc by mouth with 100 cc of 20 per cent dextrose solution administered intravenously. Urinary output had been 60 cc. Routine measures such as hot packs to the loins, xanthine diuretics and hypertonic solution of glucose had been employed in an attempt to promote secretion of urine.

During the next three days, despite moderate but adequate fluid intake and the measures described previously, output of urine had been less than 100 cc in the next twenty-four hours with an average of 60 cc daily. There had been progression of facial and peripheral edema, increase of nausea with vomiting, and some degree of mental confusion. Values for nonprotein nitrogen and creatinine had been

steadily increasing and alkalosis with depletion of the plasma chlorides had been developing (table 12)

The patient was admitted to the Clinic six days after the transfusion reaction had occurred. On admission, she was oriented and rational but slightly confused and somewhat drowsy. Her temperature was 99.2° F., pulse rate 60 beats per minute and blood pressure 110 mm. of mercury systolic and 60 mm. diastolic. There was no obvious peripheral edema except for mild puffiness about the eyes. Examination of the heart and lungs was negative to percussion and auscultation. There was mild tenderness in the right flank posteriorly and suprapubically but no organs nor masses could be palpated. Pelvic examination was deferred. Urinalysis revealed a specific gravity of 1.014, albumin graded 4, erythrocytes graded 2 (on the basis of 1 to 5) and 8 leukocytes per high dry field. The concentration of hemoglobin was 7.8 gm. per 100 cc. of blood (52 per cent), erythrocytes numbered 2,430,000 and leukocytes 14,700 per cubic millimeter of blood. Coagulation time was six minutes. The erythrocyte sedimentation rate by the Westergren method was 135 mm. in one hour. Blood urea was 214 mg. per 100 cc. of blood.

Although excretion of urine had not completely ceased, since the output on the day of admission was 110 cc., in view of severe oliguria of four days' duration, mounting nonprotein nitrogen and creatinine levels, and clinical symptoms suggesting impending uremia it was decided to institute peritoneal lavage the following morning. The patient was given 1,000 cc. of 5 per cent dextrose in distilled water intravenously; her blood was typed and cross-matched for transfusion and an indwelling urethral catheter was installed. Antibiotic therapy was likewise started (30,000 units of penicillin and 120,000 units of streptomycin every three hours administered intramuscularly). Pertinent laboratory data are given in table 12.

Lavage Period—Lavage was instituted on the second day in the hospital using modified "P" solution to which 10,000 units of penicillin and 1 mg. of heparin per liter had been added.

During the next four days dialysis proceeded in an uneventful manner with marked subjective improvement, rapid decrease of the blood urea level and almost immediate increase of urinary output, and without clinical evidence of peripheral or pulmonary edema (fig. 116 and table 13). Temperature remained between 99.6° and 101° F. with a pulse rate of 90 to 100 beats per minute. On the day after lavage had been begun the patient experienced a mild chill without rise of temperature after receiving 125 cc. of blood plasma intravenously but recovered quickly as soon as the infusion of plasma was discontinued. Accordingly it was decided henceforth to rely entirely on transfusions of cross-matched whole blood for

TABLE 12
CHEMICAL COMPOSITION OF BLOOD IN CASE 3

Miliequivalents per liter*											
	Day	Urea, mg per 100 cc of blood	Creatinine, gm per 100 cc of blood	Protein, mg per 100 cc of serum	Sulfate (serum)	Chloride (plasma)	HCO ₃ ⁻ (CO ₂ Combining Power) (plasma)	Sodium (serum)	Potas- sium (serum)	Calcium (serum)	Phos- phate (serum)
Pre-lavage period	5†	62.5†	6.9								
	4†	69.0†	9.9								
	3†	81.0†	9.9								
	2†	81.0†	9.9								
Lavage period	1	214		5.2	6.2	75.6	31.1 28.1 32.9	128	7.3	1.1	6.2
	2	198		5.2		81.6	26.1				
	3	162			3.4	82.6	26.5	133	6.6	1.1	5.4
	4	132	10.5	4.5		81.6	28.7				
	5	105		4.3	1.8	87.7	29.4	138	1.7	1.0	4.0
	6	78	6.1	4.1		93.0	31.4				
	7	58				93.7	29.1				
Postlavage period	8	71		4.5	1.6	97.3	30.6	137	3.3	1.0	2.4
	9	62		4.5		104.1	26.1				
	10	52	2.2	4.9		99.3	21.8				
	11										
	12										
	13	54	1.3	6.6	1.0	100.9	21.4				
	14										
	15										
	16										
	17	33									
	18	37		7.3	0.8	101	27.5	141	5.1	4.9	1.9

* For normal miliequivalent values of blood plasma, consult figure 131

† Days before admission to the Clinic

‡ Nonprotein nitrogen

protein replacement as well as to combat her severe anemia. In the next five days she received daily blood transfusions of cross-matched whole citrated blood, a total volume of 1,500 cc. being given.

On the fourth day of lavage, about 4 15 p m, a temperature of 103.5° F developed and the patient complained of abdominal discomfort and tightness in her thorax. Examination of the lungs revealed moist rales in both bases with bronchial breathing over the left base posteriorly. It was felt that acute pulmonary edema had

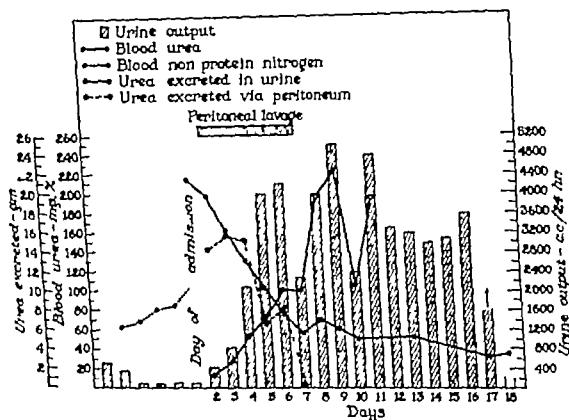


Fig 146 (Case 3) —Course of azotemia, daily urea excretion via the kidneys and the peritoneum and daily urine volume.

developed, and a roentgenogram of the thorax made with a portable apparatus confirmed this clinical impression. The patient had received 500 cc. of 10 per cent solution of dextrose intravenously earlier in the afternoon and 1 000 cc. of 10 per cent solution of dextrose the day previously for the purpose of improving her nutritional state. The pulmonary edema developed after she had received 50 cc. of whole blood. Transfusion was immediately discontinued and the patient was placed in an oxygen tent, rapidly digitalized and given 10 cc. (3¾ grains [0.21 gm]) of solution of aminophylline intravenously. Four hours later, her condition had shown marked improvement, her temperature was falling, and there appeared to be less moisture in the lung bases. As a result of hypertonic dextrose therapy, she experienced marked diuresis and excreted 2 900 cc. of urine in the next twenty hours. The coagulation time on this date was 13 minutes.

The following day the patient was given 200 cc. of whole blood

TABLE 13
UREA EXCRETION VIA PERITONEUM AND KIDNEYS IN CASE 3

Pre- lavage period	Day	Blood Urea, mg per 100 cc	Dialysate			Urine		
			Outflow, cc in 24 hr	Total Urea, gm	Urea, mg per 100 cc	Output, cc	Total Urea, gm	Urea, mg per 100 cc
	1	214						
Lavage period	2*	198	15,905	14 3	89 9	433	1 3	310 4
	3	162	19,150	15 8	82 5	821	2 9	347 8
	4	132	28,510	15 3	53 6	2,135	5 4	254 2
	5	105	24,910	6 9	27 8	4,015	7 3	181 9
	6	78	27,690	8 3	29 9	4,215	10 2	241 8
	7†	58	1,520	0 3	23 5	2,298	10 2	443 0
Postlavage period	8	71				3,925	19 7	500 8
	9	62				4,976	22 4	149 4
	10	52				2,130	10 8	413 0
	11					1,810	19 6	404 5
	Total		117,715	60 9		30 091	109 8	

* Determinations on dialysate based on twenty hour total only

† Determinations on dialysate based on two and a half hour total only

without reaction. Late that afternoon and again during the night, increase of basal rates was noted with associated tachycardia, although the patient did not manifest a rise of temperature, dyspnea or cyanosis. On two occasions within twelve hours 1,000 cc of 5 per cent solution of dextrose in distilled water were run through the peritoneal cavity, with rather dramatic decrease of auscultatory evidence of pulmonary moisture and a fall of the pulse rate from 110 beats per minute to 90.

The following morning dialysis was discontinued. Culture of the peritoneal fluid negative heretofore, was reported positive for *Escherichia coli*.

Although we were not certain at that time that renal function had improved sufficiently despite adequate urinary output to prevent recurrence of uremia, this risk seemed less than that of encountering more serious complications such as fatal pulmonary edema or bleeding.

Postlavage Period—After discontinuance of dialysis, the patient was allowed unrestricted fluids by mouth, and administration of a liquid diet with no salt restrictions was started. Fluid intake was augmented with parenterally injected fluid (5 per cent of dextrose in 0.9 per cent solution of sodium chloride) during the next three days, after which time her oral intake was sufficient in volume to accommodate her needs.

Twenty four hours after lavage had been discontinued, coagulation time had returned to six minutes. Because cultures of the peritoneal washings obtained on the fifth day of dialysis were positive for *Pseudomonas*, antibiotic therapy was continued for forty-eight hours after cessation of lavage, although at no time were clinical signs of peritonitis evident.

Diet was advanced to a soft and then to a general diet as rapidly as the patient could tolerate it, and she was allowed out of bed on the eleventh day in the hospital four days after lavage had been discontinued. A roentgenogram of the thorax was reported negative on this date. Her recovery from then on was rapid and without incident and she was dismissed from the hospital on the eighteenth hospital day. At the time of dismissal a routine urinalysis showed a specific gravity of 1.006, albumin graded 1, with negative results of microscopic examination. The concentration of hemoglobin was 10.9 gm per 100 cc. of blood (72 per cent) with 3,880,000 erythrocytes and 4,800 leukocytes per cubic millimeter of blood.

One month later the patient's local physician reported that she was entirely asymptomatic and had a concentration of hemoglobin of 12.0 gm per 100 cc of blood with 1,000,000 erythrocytes per cubic millimeter of blood.

Comment—In most respects lavage in this case was the most successful of any attempted by us and it was our sym-

pression that this may have been due to the use of modified "P" solution. The patient appeared more comfortable during the lavage period than did the previous 2 patients, and we were able to maintain a higher rate of flow without discomfort. We interpreted this as being due possibly to action of the citrate in the solution in inhibiting formation of fibrin on the intestinal coils with decreased tendency to matting and channeling.

"P" solution was modified in an attempt to correct its high alkalinity (pH 8.1). It was found, however, that modified "P" solution has a pH of 8.4, making it necessary to adjust the pH to 7.5 with citric acid before use. One observation in the present case has raised a question in our minds as to the advisability of using modified "P" solution as an irrigating fluid. The return of the blood electrolytes to normal or near normal levels during the period of dialysis leads us to feel that modified "P" solution likewise fulfills the criteria for a satisfactory irrigating fluid from the standpoint of electrolyte balance (fig. 147). However, although electrolytically it is in satisfactory balance with normal blood plasma, the prolongation of the coagulation time of the patient's blood makes it apparent that sufficient citrate was absorbed from the peritoneal cavity to alter the coagulability of the blood significantly.

Pulmonary edema was inadvertently induced on the fourth day of lavage by the intravenous use of dextrose in 10 per cent solution for the purpose of augmenting the patient's nutritional state. We feel that this solution increased the osmotic pressure of the blood sufficiently over that of the irrigating fluid to cause diffusion of water from the peritoneal cavity into the blood stream with resultant hydremia and pulmonary edema. We feel that this factor, rather than that of reaction to transfusion, was responsible for the complication because she had received 1,050 cc of cross-matched whole blood without incident prior to this episode, 250 cc of this amount being from the same donor as that which was being administered at the time when pulmonary edema occurred. Except for this incident, fluid balance in this patient appeared to be satisfactory. As in cases 1, 2 and 4, there was considerable discrepancy between the volume of fluid entering the

peritoneum and the volume recovered, which we feel can be largely explained (except in case 1) on the basis of leakage around the tubes (table 14)

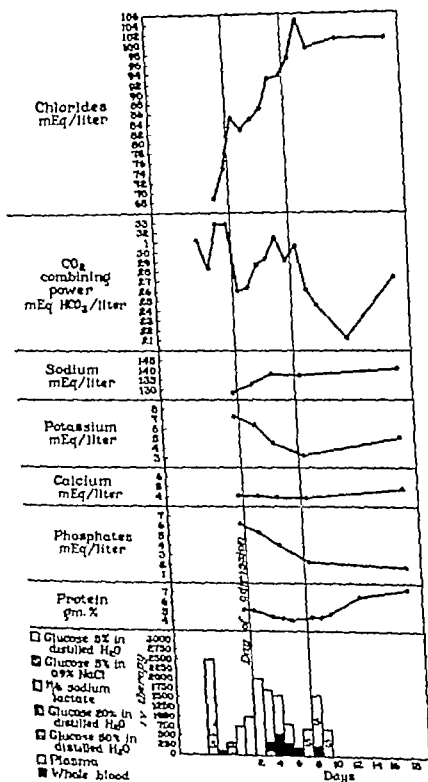


Fig 147 (Case 3) —Trend of the various constituents of the blood showing effects of parenteral administration of different fluids on daily electrolyte balance

For the further reduction of the possibility of critical pulmonary edema we employed a device first employed clinically by Balózs and Rosenak and more recently used by Muirhead

TABLE 14
APPROXIMATE FLUID BALANCE (Cc. IN 24 Hr.) IN CASE 3

	Day	Intake										Dialysate		Output		
		Intravenous														
		Oral	5% Dex- trose in		Dextrose		0.9% NaCl	M/6 Sodium Lactate	Plasma	Whole Blood	Total	Inflow	Out- flow	Urine	Emesis	Total
			Dis- tilled H ₂ O	0.9% NaCl	20%	50%										
Prelavage period	6*	1,200								1,200			500	50	550	
	5*	2,510								5,010			350		350	
	1*	1,800								1,900			60		60	
	3*	575								875			62		62	
	2*	505								1,255			85	615	700	
	1	210	1,000			10		750		1,250			110	235	345	
	2		2,000							2,000	19,100	15,905	433		433	
	3	1,050	1,100							2,750	23,580	19,150	824		824	
	4	1,640	1,000†					125	175	3,215	35,100	28,510	2,135		2,135	
	5	1,635	500†						575	2,435	28,220	24,940	4,015		4,015	
	6	2,120							300	2,620	37,500	27,690	4,215		4,215	
	7	1,310							200	1,960	1,300	1,520	2,298		2,298	
	8	1,815							250	3,415			3,925		3,925	
	9	2,950								3,590			4,976		4,976	
	10	1,975								1,975			2,430		2,430	
	11	2,850								2,850			4,840		4,840	
	12	2,700								2,700			3,325		3,325	
	13	1,700								1,700			3,200		3,200	
	14	3,600								3,600			3,050		3,050	
	15	1,200								1,200			3,150		3,150	
	16	2,100								2,100			3,625		3,625	
	17	2,750								2,750			1,600		1,600	
	Total	38,795	5,900	3,110	300	100	10	875	1,500	52,650	144,800	117,715	49,208	900	50,108	
		Total intake 107,450														

Total intake 197,150 cc

Total output 167,823 cc

* Days before admission to the Clinic

† Ten per cent dextrose in distilled water

and associates⁴⁷, namely, the "washing out" of fluid and electrolytes via the peritoneum by a hypertonic solution—5 per cent solution of dextrose in distilled water. Since, however, such a solution does not contain any electrolytes, serious depletion of electrolytes may result if the measure is employed too frequently over too long a period. Murhead and associates⁴⁷ removed 60 to 70 gm of sodium chloride in twenty-four hours by lavaging the peritoneum with 5 per cent solution of dextrose. This is simply a clinical application of the experiments of Darrow and Yannet, and is not recommended for use except in extremely emergent situations, for such a measure is fraught with possible dangerous shifts of fluid and electrolytes under certain conditions.

CASE 4 —*Prelarage Period*—The patient, a man aged 49 years, was admitted to the Clinic with a lesion in the upper lobe of the right lung discovered in a routine roentgenogram of the thorax taken three months previously. A diagnosis had been made of probable bronchogenic carcinoma with atelectasis and abscess.

Physical examination revealed a blood pressure of 138 mm of mercury systolic and 94 mm diastolic. The pulse rate was 112 beats per minute and the temperature was 98° F. Breath sounds appeared to be increased over the upper lobe of the right lung and the diaphragm did not appear to move on the right side. Except for the foregoing findings the results of physical examination were essentially negative.

Results of routine urinalysis were entirely negative and the blood urea level was 30 mg per 100 cc. The concentration of hemoglobin was 14.5 gm per 100 cc. of blood (96 per cent) with 4,740,000 erythrocytes and 8,300 leukocytes per cubic millimeter of blood. Roentgenograms of the thorax revealed a fibrotic lesion in the upper lobe of the right lung with considerable retraction of the apical portion of the lung. The lesion was felt, on the basis of roentgenographic evidence, to be tuberculous in origin, although smears and cultures of sputum and gastric washings were reported negative for acid fast bacilli. Sputum was also reported negative for malignant cells.

Bronchoscopy, performed two days after admission to the Clinic, revealed a stricture of the bronchus of the upper lobe of the right lung of indeterminate nature. Bronchial smears did not reveal malignant cells and pathologic report of tissue removed from the bronchus of the upper lobe of the right lung in the region of the stricture was reported as 'inflammatory tissue.

In view of the indeterminate nature of the lesion in the right upper lobe, exploration of the right lung was advised. The patient entered the hospital three days after admission to the Clinic, and nine days later the right thoracic cavity was explored. Adherence of the parietal to the visceral pleura over an atelectatic right upper lobe was found, and right upper lobectomy was done. The pathologist reported a benign inflammatory bronchial stricture with an airless contracted pulmonary lobe peripheral to the stricture. The patient withstood operation satisfactorily, although it was necessary for him to receive 1,000 cc of whole citrated blood. After operation, he became moderately cyanotic, but was relieved by removal of considerable bronchial secretion by suction through a bronchoscope and administration of oxygen.

Although the patient's general condition improved considerably after surgical intervention, he became oliguric the day after operation. An indwelling urethral catheter was installed but in the next five days, the twenty-four hour urinary output ranged between 20 and 60 cc. Conservative measures were employed during this period in an attempt to induce spontaneous resumption of renal function but to no avail. With the development of acute urinary suppression, retention of urea, sulfate, phosphate, and other end products of protein metabolism was noted, and on the fourth day nausea, vomiting and drowsiness were observed. Significant laboratory data are recorded in table 15.

Lavage Period—On the fifteenth day in the hospital, because of progressive renal insufficiency and signs of clinical uremia, it was decided to attempt peritoneal lavage. The procedure was carried out according to the method described before, "P" solution buffered to pH 7.6 being used as irrigating fluid with the addition of 10,000 units of penicillin and 1 mg of heparin per liter. The patient had received 30,000 units of penicillin every three hours intramuscularly since the operation, and at this point 120,000 units of streptomycin administered intramuscularly every three hours were added.

Lavage was carried out satisfactorily and without incident for seventy-two hours. Clinically the patient looked much improved, although pulse and temperature continued elevated (temperature 101° to 103° F., pulse 100 to 120). The blood urea level dropped 90 mg per 100 cc in this period (fig 148). Throughout the lavage period, supplemental parenterally administered fluid consisted of 1,500 to 2,000 cc daily of 5 per cent solution of dextrose fortified with vitamins B and C, with the addition of 7 grains (0.45 gm) of aminophylline (table 16).

On the evening of the third day of lavage, profuse leakage of fluid around the inflow tube was encountered, and little or no dialysate could be recovered from the outflow tube by suction. Lavage was stopped, for it was suspected that a pocket had formed

TABLE 15
CHEMICAL COMPOSITION OF BLOOD IN CASE 1

	Day	Urea mg per 100 cc of blood	Creatinine mg per 100 cc of blood	Protein gm per 100 cc of serum	Milliequivalents per liter*						Calcium (serum)	Phos- phate (serum)
					Sulfate (serum)	Chloride (plasma)	HCO ₃ ⁻ (CO ₂ Combining Power) (plasma)	Sodium (serum)	Potas- sium (serum)			
Preliminary	5	30				97.6	26.1					
	11	64				95.9	22.7					
	12	116	7.8			91.2	25.7					
	13	192	12.5	6.85		89.6	24.4					
	14	210	15.7			93.0	23.1					
Layago	15	238	19.2	6.85	11.6	94.9	21.1		6.3		1.3	1.7
	16	272		5.95		91.9	21.1					
	17	198	13.2	5.95		102.9	22.7				1.3	1.5
	18	228	18.5	6.18		98.1	24.8					
	19	216	18.5	6.3	7.8	91.2	20.6	119.1	7.7		1.1	5.6
	20	306	23.0	6.18		96.9	17.2					

* For normal milliequivalent values of blood plasma consult figure 13-4

around the inflow tube. Reversal of the flow failed to re-establish satisfactory flow, and it was necessary to insert a catheter through a trocar in the left lower quadrant of the abdomen, in order to establish satisfactory flow of fluid through the peritoneal cavity. After this, lavage was resumed and a satisfactory rate of flow was accomplished. Despite this, the level of urea in the blood steadily increased (fig 148) and the patient's condition began to deteriorate. Oliguria persisted, drowsiness increased to stupor, and frequent muscular twitchings developed. On the fifth day after lavage had

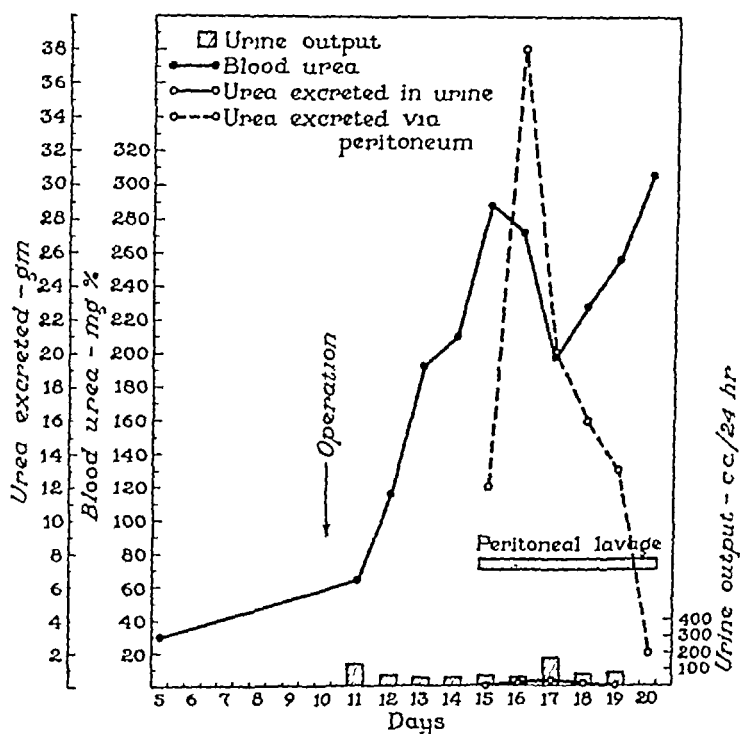


Fig 148 (Case 4) —Course of azotemia, daily urea excretion via the kidneys and the peritoneum, and daily urine volume

been started, moist rales were heard in both lung bases, and the patient sank into a deep stupor and died.

Necropsy Report —At the time of the postmortem examination there was edema of the ankles, grade 1+, and edema of the sacrum and back, grade 1. The peritoneal cavity contained 50 cc of cloudy yellow fluid. The intestinal coils were dull in appearance and the omentum was adherent to a considerable portion of the small intestine and the right lateral abdominal wall, and to the abdominal wall in the left upper quadrant of the abdomen around the site of the inflow tube. The omentum, together with old adhesions and

TABLE 16
APPROXIMATE FLUID BALANCE (CC. IN 24 Hrs.) IN CASE 4

APPROXIMATE FLUID BALANCE (Cc. in 24 Hrs.) IN CASE 4													
	Day	Intake						Dialysate		Output			
		Oral	Intravenous				Total						
			Dextrose in Distilled Water		Dextrose 5% in 0.9% NaCl	Whole Blood							
			5%	10%				20%					
Pre-lysis period	10		800				900	1 700			135	250	385
	11	520	1 150	1 000			500	3 170			65	275	340
	12	565	1 000					1 565			50	150	200
	13	960	2 000					2,960			50	325	375
	14	475			250			1 725					
Lavage period	15		1 500					1 500	12 000	9 820	60		60
	16		1 500					1 500	30 500	22 960	41		41
	17		1,500					1 500	21 050	13 790	156		156
	18		2,000					2,000	23 825	23,190	64		64
	19		1 100					1 400	20 150	18 360	80		80
	20				250				6 000	7 120			
		2,520	12,850	1 000			1 400	19 020	116 525	95,240	701	1 000	1 701
	Total												

Total intake 135 545 cc.

Total output 96 941 cc

with the other organs, formed a pocket which opened into the incision in the left upper quadrant and appeared to have no other exit. The peritoneum was dull in appearance and there were multiple flecks of fibrin on its surface. There was no free fluid in the pleural cavities and pulmonary congestion in both lower lobes was graded 1+ on the basis of 1 to 4. Both kidneys appeared to be increased in size and their consistency was somewhat flabby. The kidneys appeared swollen and edematous on cut section and the cortex was pale pink. There were multiple submucosal hemorrhages in the calices, pelvis and ureter of the left kidney.

Histologic examination of the peritoneum revealed evidence of mild chronic organizing peritonitis. The exudate was not purulent and organisms were not demonstrated in large amounts. While one could not definitely establish the nature of the peritonitis, it was the opinion of the pathologist that the reaction demonstrated was preponderantly chemical in nature rather than bacterial.

Sections of the lungs revealed edema, congestion in the inter-alveolar tissue and a few regions of hemorrhage.

Sections of the kidneys were said to show a microscopic picture classic in nature for so-called hemoglobinuric nephrosis. Pigmented casts were seen in the lower portion of the convoluted tubular system and collecting tubules. Regions were seen in which hyaline casts were present in the convoluted tubules. There was evidence of interstitial inflammatory reaction with collections of lymphocytes. Granulomatous reaction was seen around many of the hyaline casts, some of which had been extruded into the interstitial tissue. In addition, there were varying degrees of degeneration in the tubular epithelium.

The final pathologic diagnosis was (1) stenosis of the bronchus of the upper lobe of the right lung with atelectasis, (2) recent abdominal incisions (left upper quadrant and right lower quadrant) for peritoneal lavage, (3) uremia, (4) pulmonary congestion (5) peritonitis (chemical?).

Comment—The immediate cause for renal suppression in this case, as in cases 1 and 2, is open to question. It is possible that operative shock and renal anoxia during the episode of cyanosis immediately after the operation were contributory factors. However, the episode of cyanosis was of short duration and was quickly relieved by bronchial aspiration and administration of oxygen. It is possible that transfusion reaction may have been a factor, and the presence of granules of hemoglobin in some of the tubules noted on histologic examination lends support to this possibility. However, no clinical signs of transfusion reaction were noted and the blood

received was compatible blood insofar as both blood grouping and Rh factor were concerned. We have occasionally encountered acute urinary suppression after abdominal or pelvic operations, but this is the first time that we have encountered such a situation after a thoracic surgical procedure.

This case represents, further, a complication to peritoneal lavage not previously encountered by us, namely, that of channeling and pocketing about the inflow tube with the loss of adequate surface for successful dialysis. The patient previously had undergone cholecystectomy, and at necropsy was found to have multiple intra-abdominal adhesions, which undoubtedly contributed to the formation of the pocket.

Lavage was progressing satisfactorily with noticeable clinical improvement in the patient's condition until the evening of the third day, when the pocket closed. Up to this time, the levels of retention products in the blood had been falling steadily (table 15), and large amounts of urea had been recovered in the dialysate (table 17). After re-establishment of flow through the peritoneum, however, despite maintenance

TABLE 17
UREA EXCRETION VIA PERITONEUM AND KIDNEYS IN CASE 4

	Day	Blood Urea mg. per 100 cc	Dialysate			Urine		
			Outflow cc in 24 hr	Total Urea gm	Urea mg per 100 cc	Out put cc	Total Urea gm	Urea mg. per 100 cc.
Prelavage period	5	30						
	11	61						
	12	116				135		
	13	192				65		
	14	210				50		
Lavage period	15	288	9 820	11.9	121.1	60	0.6	113.2
	16	272	22 960	30.1	166.1	41	0.14	232.1
	17	198	13 790*	20.2	146.5	156	0.21	125.0
	18	2*8	23 190	16.2	69.9	64	0.12	121.0
	19	216	18 760	12.8	69.4	20	0.23	200.2
	20	306	7 120†	1.8	2.3			
	Total		95 210	101.0		301	0.21	

* Incomplete.

† One four hour specimen daily.

of what should have been an adequate rate of flow, urea levels mounted steadily and excretion of urea via the peritoneum decreased markedly. In reality, the result was as if lavage had been discontinued prematurely on the third day.

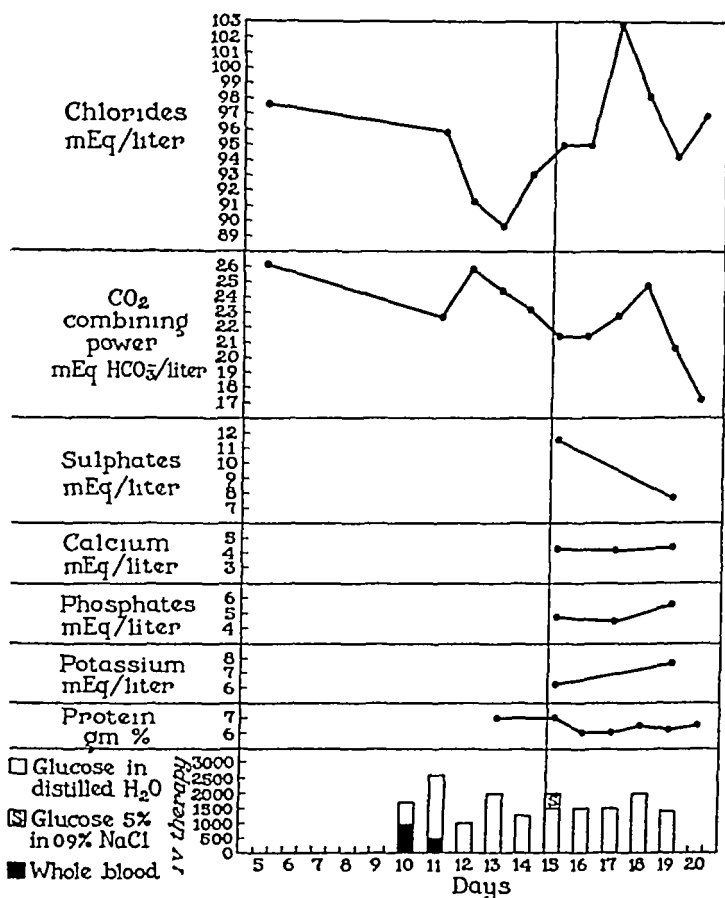


Fig 149 (Case 4) —Trend of the various constituents of the blood showing the effects of parenteral administration of different fluids on daily electrolyte balance

Electrolyte balance was reasonably well maintained across the peritoneum (fig 149). However, both chloride and plasma bicarbonate levels were persistently slightly subnormal. This, in our opinion, was due to impairment of the dialyzing membrane by channeling.

GENERAL COMMENT

From the foregoing discourse and report of cases, it can be seen that peritoneal lavage, although established clinically as

a means of treating acute renal failure with anuria and uremia, is not without certain hazards and complications, some of which may be serious. Because of this, and since, at best, in patients with advanced organic renal disease it can lead only to temporary clinical improvement, its use as a therapeutic measure should be restricted to those cases in which acute renal failure is associated with reversible renal lesions.

The risk of lethal peritonitis, although small, nevertheless remains a factor with which to reckon. Peritoneal contamination appears to occur in a large percentage of cases, whether or not a bacterial filter is used in the system. Whether or not the use of improved peritoneal tubes will reduce the incidence of peritoneal infection remains to be seen. There can be no doubt that the antibiotic agents, penicillin and streptomycin, added to the irrigation fluid and administered parenterally are of the utmost importance in control of this complication.

Difficulties in the maintenance of adequate electrolyte and water balance on both sides of the dialyzing membrane constitute the greatest hazards. It has been shown repeatedly that this balance is extremely delicate, and minor changes of technic, composition of fluid or parenteral therapy may produce rapid and in some cases deleterious consequences. The complications of severe dehydration, electrolyte depletion and overhydration with massive peripheral or pulmonary edema are of such magnitude that they cannot be underestimated.

Channeling and pocketing of the omentum and intestinal coils about either the inflow or the outflow tube, with disruption of the flow of peritoneal fluid and reduction of the dialyzing surface, constitute a further complication to the procedure. Perhaps the reduction of the incidence of peritoneal contamination and infection and the addition of heparin to the irrigating fluid in increased amounts will, to a great degree aid in combating this hazard. There is no doubt that intra-abdominal adhesions resulting from previous abdominal operations will aggravate and tend to promote such a disastrous development.

Yet, if the foregoing possibilities are borne constantly in mind the results achieved often justify the risks involved. The procedure itself is basically simple, and the apparatus

can be constructed and assembled in any hospital Facilities for preparing sterile perfusion fluid in large amounts must be available, as well as an adequate clinical laboratory for analysis of blood counts, chemical examination of the blood and the other indicated studies Beyond this is needed an interested clinician, informed as to the basic physiology of the peritoneum as a dialyzing membrane and as to the water and electrolyte requirements of the patient, and with mind and eye alert for the development of complications

In summary, it is our opinion that when acute suppression of renal function with increasing renal insufficiency develops, several days of routine intravenous therapy and supportive measures should first be employed in an attempt to promote formation of urine If, at the end of this time, conservative measures have failed, and it appears that fatal termination of the case may result, then the procedure of peritoneal lavage should be initiated as a lifesaving measure

ACKNOWLEDGMENT

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METHODS OF CHEMICAL ANALYSIS EMPLOYED IN THE PRESENT STUDY

WHOLE BLOOD

Hemoglobin

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DIALYSATE

Total nitrogen

Kjeldahl, J Neue Methode zur Bestimmung des Stickstoffs in organischen Körpern Ztschr f anal Chem 22 366-382, 1883

Urea

Same method as for estimation in whole blood and serum

Nonprotein nitrogen

Macro Kjeldahl method on filtration after precipitation of protein with Folin's tungstic acid reagent.

Total protein

Macro-Kjeldahl method for estimation of total nitrogen Estimation of nonprotein nitrogen by macro-Kjeldahl method after precipitation of the protein by Folin's tungstic acid reagent method Total proteins calculated by subtraction of the nonprotein nitrogen from the total nitrogen and multiplication of the remainder by 6.25

URINE

Total nitrogen

Same method as for estimation in dialysate

Urea

Same method as for estimation in whole blood or serum

Nonprotein nitrogen

Same method as for estimation in dialysate

Total protein

Same method as for estimation in dialysate

Chloride

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THE ADMINISTRATION OF ANTIBIOTIC PREPARATIONS BY THE AEROSOL METHOD: A CRITICAL EVALUATION*

ARTHUR M. OLSEN

AEROSOLS are mists of medicated solutions. When such mists are inhaled by a patient, the treatment is called aerosol therapy. Aerosols usually are produced by the forceful passage of air or some other gas through a nebulizer which contains the solution to be nebulized. In 1919 Heubner reported that a solution must be broken into very fine particles if the medication is to penetrate the bronchioles and alveoli.

Much of the pioneer work in the field of aerosol therapy was done by Barach and his associates. Much credit also should go to Castex, Capdehourhat and their associates in Argentina, who have worked with aerosols for many years.

Many different drugs have been administered by the method of inhalation. In the earlier years, the various bronchodilator substances were used extensively. In 1935 Graesser and Rowe demonstrated that epinephrine in 1:100 solution could be nebulized and inhaled by the patient with acute asthma and that a very beneficial result could be obtained. Solutions of sulfonamides were nebulized, especially in the treatment of pulmonary suppurative diseases. Unfortunately, the action of sulfonamides is inhibited in the presence of purulent exudates. Aerosols of promin were used in the treatment of tracheobronchial tuberculosis at the Clinic in 1941.¹ Brown Sansome and Laskin demonstrated that solutions of penicillin could be aerosolized and that the drug was absorbed from the lungs and excreted in the urine in substantial quantities. Subsequently, at the Clinic² it was found that streptomycin could be nebulized either alone or in combination with penicillin. For about ten years aerosol therapy has been used widely in a variety of conditions.

Many different types of equipment have been used to pro-

* Read at the meeting of the Section in Medical Science, American Association for the Advancement of Science, Chicago, Illinois, December 26 to 31, 1944.

duce therapeutic aerosols The most commonly employed apparatus consists of a glass vessel called a nebulizer A medicated solution placed within this vessel is made into a fine mist by a stream of air or oxygen which passes through the vessel and forces the liquid against a glass baffle In a properly constructed unit the size of the majority of the

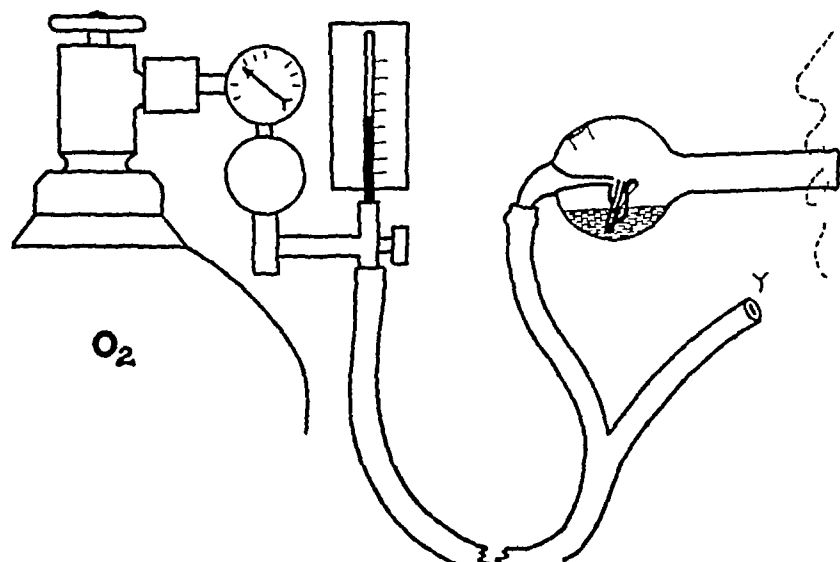


Fig 150 —One type of apparatus used for nebulization therapy Oxygen is used as the source of positive pressure, 4 to 6 liters per minute are required The Y tube is closed during inhalation and is opened during exhalation In this drawing the "vaponefrin" type of nebulizer is depicted (Reproduced, with the permission of the publishers, from Olsen, A M Nebulization therapy in bronchiectasis the use of penicillin and streptomycin aerosols J A M A 134 947-952 [July 12] 1947)

particles produced will be in the 0.5 to 2 micra range The optimal size of a particle for penetration into the smaller bronchioles and alveoli is approximately 1 micron Larger particles will be deposited on the mucous membranes of the mouth, hypopharynx, trachea and large bronchi The tiniest particles are likely to be exhaled with the expired air A number of commercial nebulizers have proved to be satisfactory, one of these is the vaponefrin nebulizer

The simplest apparatus consists of a nebulizer connected to a tank of oxygen or compressed air The many modifications of this apparatus (fig 150) are designed to conserve the

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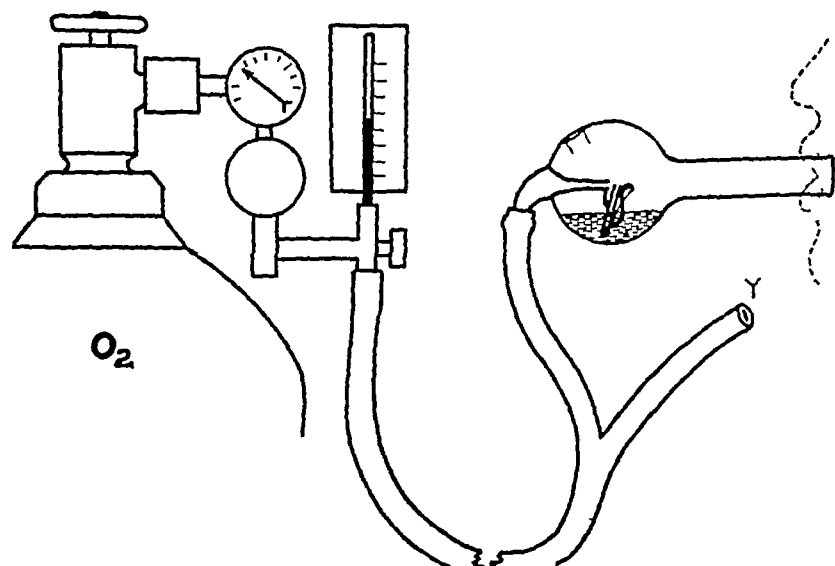


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The simplest apparatus consists of a nebulizer connected to a tank of oxygen or compressed air. The many modifications of this apparatus (fig 150) are designed to conserve the

drug, to make the process of inhalation easier for the patient and to prevent local reactions in the mouth of the patient. Thus the use of a Y tube permits nebulization during the inspiratory phase of respiration. Various types of rebreathing apparatus help to conserve the drug. An automatic demand apparatus has been devised which is an aid to the patient in taking his treatment. The nebulizer may be attached to masks or hoods for ease of administration. The humidification of oxygen as it leaves the tank reduces the local reaction in the mouth. Both Barach, and Segal have shown that a higher concentration of penicillin in the blood can be obtained if a warm, humidified aerosol is produced. The use of a hand-operated or foot-operated tire pump has been advocated for home treatment and has been found to be satisfactory by some patients.

An entirely different method of producing aerosols has been devised by Prigal. He described a combined steam generator and aerosolizer which produces warm, moist aerosols. I have had no experience with this method but Prigal stated that very satisfactory concentrations of the drug used in the blood are obtained.

Barach devised a method of treating sinusitis by the inhalation of penicillin aerosol directly into the nostrils. His apparatus provides for negative pressure in the sinuses. I have had no personal experience with the treatment of sinus disease, but the method described has been used by several investigators with good results.

This presentation is concerned primarily with the administration of antibiotic aerosol and I shall attempt to evaluate the efficacy of giving penicillin and streptomycin aerosols. Penicillin has been used extensively as an aerosol and much information is available concerning its absorption and excretion and its therapeutic effect on a variety of disease processes. Penicillin usually is dissolved in physiologic salt solution and is used in concentrations varying from 10,000 to 100,000 units per cubic centimeter. Both penicillin sodium and calcium salts have been used. However, the crystalline penicillin in the form of the sodium or potassium salt now is considered to be the most satisfactory preparation. Bryson and his co-workers

were able to recover from the urine 60 per cent of the penicillin administered by means of inhalation to normal healthy adults. Concentration of penicillin in the blood varies considerably, but values commonly fall between 0.05 and 0.10 units per cubic centimeter one hour after the inhalation of 50,000 units per cubic centimeter.

At the Clinic we have had considerable experience with streptomycin as an aerosol. We have used streptomycin hydrochloride in concentrations varying from 0.025 to 0.1 gm per cubic centimeter of physiologic saline solution. Concentrations in the blood have been negligible and only minute quantities of the drug have been recovered from the urine.

On the basis of our present knowledge at the Clinic, we cannot advocate the use of the aerosol therapy of diseases other than those affecting the respiratory tract. Although penicillin reaches the blood through the alveoli, the concentrations obtained are variable, uncertain and dependent on the efficiency of the subject in inhaling the drug. The absorption of streptomycin through the pulmonary circulatory system is almost nil. Hence, the administration of antibiotic aerosols cannot be recommended as a substitute for the parenteral administration of antibiotic preparations.

If antibiotic aerosol therapy has merit, it is because of the topical effect exerted by the inhaled preparations on the bronchial mucosa and the mixing of these drugs with purulent bronchopulmonary secretions. There is considerable evidence to indicate that penicillin and streptomycin aerosols do have a demonstrable local effect on bronchial infections. In our experience this is best illustrated in treatment of purulent bronchiectasis. In the first place, the parenteral administration of penicillin and streptomycin has not proved to be beneficial in a considerable number of cases of bronchiectasis. Injections of these drugs have not materially reduced the volume of pulmonary secretions, it is usually impossible to recover any of these antibiotics from expectorated material, repeated cultures of the sputum after intramuscular injections have failed to reveal any significant alteration in the bacteriologic content of the sputum. On the other hand, after the inhalation of these antibiotics most of our patients have ex-

perienced a marked reduction in the volume of sputum. Furthermore, both penicillin and streptomycin can be demonstrated in the sputum in significant quantities several hours after inhalation has been discontinued. In many instances bacteria have been eradicated from the sputum by a course of therapy.

gram-negative bacteria were not isolated from sputum cultures until after the patient had been treated with penicillin aerosol. Barach and others have pointed out that these gram-negative bacteria apparently elaborate a "penicillinase" which interferes with the bacteriostatic effect of penicillin.

The determination of the sensitivity of specific organisms to penicillin or streptomycin is a most important feature of the bacteriologic study of bronchial secretions. When feasible such studies were carried out before and during aerosol therapy. Bacteriologic studies are difficult and time-consuming. I am greatly indebted to Dr. Fordyce Heilman and Dr. Luther Thompson for their co-operation in this study.

Certain limitations of aerosol therapy in treatment of bronchiectasis should be pointed out. The bronchial dilatation of bronchiectasis is a permanent change and the suppurative process is a complication of damage of the bronchial tree. If the patients are not suitable for pulmonary resection, relapses may occur after cessation of therapy. Continued treatment on a modified scale is essential if improvement is to be maintained. With continued treatment, resistant bacteria are likely to appear in bronchial secretions. Gram-negative bacteria are especially likely to become resistant to streptomycin.^{5,9} The development of resistance by bacteria may well account for some of the failures in aerosol therapy and makes the treatment of recurrent bronchorrhea more difficult.

The efficacy of aerosol therapy in other bronchopulmonary conditions depends on the extent to which susceptible bacteria are responsible for these conditions. In some cases of early lung abscess it seems to have value. In asthma and emphysema the use of antibiotic aerosols is helpful only when these processes are associated with bronchial infection which can be controlled by the inhalation of antibiotics. In general, our experience with antibiotic aerosols in these conditions at the Clinic has not offered promise. Certain patients with chronic bronchitis have been helped by aerosol therapy. We cannot recommend inhalation treatment in acute virus infections of the upper part of the respiratory tract. However, in some instances in which respiratory infections have been

TABLE 1
COMMON PATHOGENIC BACTERIA FOUND IN BRONCHIECTATIC SECRETIONS*

Gram-positive	Gram-negative
Pneumococcus	<i>Escherichia coli</i>
Streptococcus	<i>Hemophilus influenzae</i>
Hemolytic type	<i>Aerobacter aerogenes</i>
Nonhemolytic type	<i>Klebsiella</i>
Staphylococcus	<i>Pseudomonas aeruginosa</i>
Micrococcus	<i>Proteus</i>

* Reproduced, with permission of the publishers, from Olsen, A M
Penicillin and streptomycin therapy for chronic bronchiectasis Minnesota
Med (In press)

be isolated from sputum cultures. The value of aerosol therapy in bronchiectasis is limited by the tendency of bronchial infections to recur and by the development of resistant strains of bacteria in bronchial secretions. Gram-negative bacteria are particularly likely to become resistant to streptomycin. Aerosols of penicillin or streptomycin are sometimes helpful in the treatment of nontuberculous lung abscess. Their value is limited by the difficulty in getting the drug into the diseased portion of the lung. Nebulization therapy may be helpful in treating patients with asthma, emphysema and chronic bronchitis only if these conditions are associated with infections of the bronchial tree caused by bacteria sensitive to the antibiotic used. Aerosols are of no value in treatment of respiratory infections caused by viruses. In general, the results of bacteriologic examinations of bronchial secretions should provide the indications for antibiotic aerosol therapy.

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THE TRANSPORTATION OF PATIENTS BY AIR

JAN H. TILLISCH

TRANSPORTATION by air causes a change in the external environment of the passenger to which the body must adjust. If the individual is sick the adjustment, if it is accomplished, is made with greater difficulty than under ordinary circumstances. It, therefore, is important that contemplated air travel for a patient be considered in light of the extent of environmental change and the patient's ability to adjust to this change. The environmental changes that take place with ascent to altitude are as follows: atmospheric pressure is decreased, with resultant lowering of the oxygen tension, expansion of gases in body cavities and evolution of gases in body fluids, and cold is increased.

The most important physical effect of going to altitude is the lowered oxygen tension in the ambient air. As a result of this lowered oxygen tension at altitude the individual has a deficit in arterial oxygen tension. This is known as "anoxic anoxia." The symptoms of acute anoxic anoxia encountered in ascent vary somewhat in different individuals. In general, however, up to 14,000 or 15,000 feet if exposure is not too prolonged, there are few, if any, symptoms of anoxia because the compensatory mechanisms of the body provide adequate defense. These compensatory mechanisms brought into play with beginning anoxia, are increased depth and rate of respiration and increased pulse rate and blood pressure. Above 15,000 feet the compensatory mechanisms no longer suffice and symptoms of anoxia develop. The most striking symptoms are retardation of mental and physical processes, impairment of the special senses, especially vision, pronounced fatigue, and frequently changes in personality such as euphoria. From 20,000 to 23,000 feet unconsciousness usually occurs. The aftereffects of anoxia are headache, lethargy, nausea and vomiting, or severe prostration. Recovery usually takes place in twenty-four to forty-eight hours.

In modern aircraft, anoxia at high altitude is prevented by the use of oxygen. The commercial transport plane usually is

equipped with a constant-flow oxygen system and a BLB mask. Many of the newer planes have pressure cabins, maintaining a constant altitude of about 8,000 feet up to an ambient pressure of 25,000 feet. Anoxia resulting from altitudes of 12,000 to 15,000 feet or above is prevented in most instances by adequate oxygen equipment. However, between 10,000 feet and 12,000 feet anoxia may be present but it is compensated for by the normal healthy individual. The sick individual may not be able to adjust as well to the oxygen want encountered at these altitudes and serious complications may arise from the additional anoxia. Altitudes between 10,000 and 12,000 feet are emphasized because oxygen may not be administered due to ignorance of the crew for its need by a sick passenger or due to the fact that planes flying with these levels as maximal altitude may not have oxygen equipment for passengers. Fortunately at the present time the usual passenger plane has satisfactory oxygen equipment. Thus in advising a patient, who already has anoxia, to fly one must take into consideration the degree of his anoxia, the degree of anoxia to which he will be exposed due to altitude and to duration of exposure, and last the presence or absence of oxygen equipment on the plane.

The second effect of decreased atmospheric pressure encountered at high altitude is the expansion of gases within the body cavities. Boyle's law states that a given quantity of gas varies in volume inversely in proportion to the absolute pressure exerted upon it. Thus a given quantity of gas at sea level will approximately double in volume when taken to 18,000 feet.

The structures most commonly affected by the expansion of gases at high altitudes are the middle ear, the sinuses, and the gastro-intestinal tract. Of these the ear is most frequently affected. As the barometric pressure is reduced during ascent, the expanding air in the middle ear causes pressure which eventually becomes sufficiently great to force the air out through the eustachian tube. The pressure within the middle ear then becomes equalized with the outside pressure. During descent the barometric pressure increases, and the pressure in the middle ear falls below that of the external air. With this

negative pressure in the middle ear it is difficult, and sometimes impossible, to open the eustachian tube "Aero-otitis media" is the term used to describe the traumatic inflammation caused by the difference in pressure between the external air and the air in the middle ear

A phenomenon similar to that which occurs in the middle ear takes place in the paranasal sinuses with changes in barometric pressure. If the sinuses are normal, air passes into, and out of, the cavities and thus produces equalization of pressure at the usual rates of ascent and descent. If the sinusal openings are obstructed for any reason, as in sinusitis, such equalization of pressure does not take place. The difference in pressure between the air in the sinuses and the external atmosphere, produces pronounced pain which may occur either on ascent or on descent

The gastro-intestinal tract normally contains varying amounts of gas. The sources of gas in either normal or abnormal amounts are swallowed air, digestion, fermentation and bacterial decomposition of food, faulty absorption of gas from the gastro-intestinal tract, and secretion of gas from the blood. Most of the gas is contained in the stomach and large intestine. During ascent the gases in the gastro-intestinal tract expand. Ordinarily, relief is obtained by belching and by the passing of flatus. In some persons, however, expansion of gas because of inadequate elimination, or entrapment of gas in the gastro-intestinal tract causes extreme discomfort.

The third effect of decreased atmospheric pressure, the generation of gases in body fluids, rarely occurs below 25,000 feet and therefore is not encountered in the transportation of patients in commercial airline or private planes. It is sufficient to say that with the marked decrease in atmospheric pressure found at 25,000 feet bubbles are found in the tissues and in the blood and other body fluids. These produce various symptoms, the most frequent of which is pain in the joints, bones and extremities which is known as the "bends."

The factor of decreased temperature occurring with increased altitude is not important in the transportation of the ill person because of the adequate heating systems of aircraft. Consideration of the environmental changes that take place

on ascent to altitude and their effect on passengers enables one to give more accurate advice concerning transport of patients by air. Diseases of the upper part of the respiratory system are seldom actual contraindications to transportation by air. Even under most severe conditions this group of diseases will only increase the susceptibility to aero-otitis media by obstruction of the eustachian tube or to aërosinusitis by obstruction of the sinusal openings so that equalization of pressure does not take place with the changes of altitude. Patients with pneumonia have an already present anoxia. If it is necessary to transport these patients by air they should be given oxygen when flying even though no evidence of respiratory embarrassment is present.

The question of flying for the patient with active pulmonary tuberculosis has not been entirely settled. The patient with far-advanced pulmonary tuberculosis or with any significant impairment of respiratory efficiency had best not fly. The most important factor to consider is whether or not he has a pneumothorax.^{5,7} The expansion of air contained in the pleural cavity as a result of the decreased atmospheric pressure encountered at altitude may cause grave or even fatal complications. The death of a patient with pneumothorax occurring as a result of transportation by air at an altitude of 16,000 feet, has been reported by Dowd. The advisability of transporting patients with other pulmonary diseases by air is dependent on the degree of respiratory embarrassment that is present.

The individual with mild asthma can usually fly without difficulty. However, if he is susceptible to frequent and severe attacks, he may encounter difficulty when taken to altitudes where anoxia occurs.

The cardiac status of the patient to be flown perhaps has been given unwarranted attention. It would seem that an individual with a mild, uncomplicated hypertension or a well-compensated valvular heart disease could fly with safety. It is believed that patients with severe hypertension and a history of complications of hypertension or with frankly decompensated valvular heart disease had best not fly. If it is necessary for these patients to fly oxygen should be administered to

them from the ground up. Numerous authors²⁶⁸ have called attention to coronary heart disease in relation to aviation. Coronary heart disease in the passenger must be handled as an individual problem. Certain generalizations may be put forth as an aid in deciding the problem. It is best not to fly for some time after a myocardial infarction. The patient with coronary sclerosis and cardiac decompensation had best not fly. This is also true for the patient with easily induced anginal attacks. The factor of nervous apprehension to flying must also be taken into consideration in reaching a decision as to the advisability of travel by air for a patient with coronary sclerosis. Another factor that must be taken into consideration is whether or not other forms of transportation may put an even greater strain on the heart. When the patient with coronary disease does fly it is best to administer oxygen at altitudes over 7,000 feet and to prescribe a mild sedative to allay nervous tension.

Diseases of the gastro-intestinal tract very seldom will contraindicate transportation by air. An individual with acute gastro-enteritis may suffer an exacerbation due to hyperirritability of the gastro-intestinal tract induced by motion of the plane and expansion of gastro-intestinal gases which occur at altitude. The patient with threatened perforation of a peptic ulcer or recent gastro-intestinal hemorrhage, who must be transported by air, should be placed in a pressurized cabin⁴ or the flight should be made at low altitude. The reason for this is that the expansion of the gastro-intestinal gases occurring at altitude may actually perforate the ulcer or increase the gastro-intestinal bleeding.

Collins has reported a case of congenital megacolon with abdominal distention which became excessive with increased altitude. This does not mean that a patient with congenital megacolon should not fly, but if extreme abdominal distention does occur the plane should be brought down to lower altitudes. Patients recovering from abdominal operations or suffering from penetrating wounds of the gastro-intestinal tract may suffer ill effects at high altitudes from the expansion of gas normally contained in the gastro-intestinal tract. As a result of this expansion, healing tissue may be torn or

gas may be forced out through unhealed openings in the intestine, thus carrying fecal material into the peritoneal cavity. For this reason Armstrong advised against transporting at high altitudes patients who have acute appendicitis, intestinal obstruction or strangulated hernia. In patients suffering from diaphragmatic hernia the viscera contained within the hernia may become strangulated as a result not only of expansion of gases within the bowel and thorax, but also of increased intra-abdominal pressure which occurs from the expansion of gas within the entire gastro-intestinal tract.

Diseases of the genito-urinary system are rarely contraindications to travel by plane. This is also true of diabetes mellitus, hyperthyroidism and hypothyroidism. Diseases of the skeletal system do not contraindicate flying unless a deformity is present which makes it difficult for the patient to sit upright as would be the case with a patient suffering from a severe osteo-arthritis of the hip or ankylosis of the hip or knee joint.

Patients suffering from recent intracranial injuries or neurosurgical procedures involving the cranium should not fly unless the plane can be flown at low altitude. This is also true of the patient who has had recent encephalography or ventriculography. The reasons for this are twofold: if there is any intracranial entrapment of air the expansion of the air with ascent to high altitudes may cause trouble, and, if there is increased intracranial pressure with secondary anoxia of the brain tissue, the condition may be made worse by the anoxic anoxia of altitude.

The psychotic patient may be difficult to control on a plane and may be dangerous to ship and crew. It has been observed that the individual with grand mal epilepsy will have convulsive seizures on a plane more frequently than under ordinary circumstances. This is more than likely due to nervous stimulation rather than to anoxia. It is not best therefore for an epileptic patient to travel by plane unless he is well controlled. The psychoneurotic patient may fly without detriment to himself except for the increased susceptibility to motion sickness.

The patient with anemia has an already present anemic

anoxia The anemic anoxia present in a moderately severe anemia is not sufficiently great to contraindicate flying The patient who has extremely severe anemia or who is in shock should not fly unless oxygen is administered

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CHANGING CONCEPTS IN TUBERCULIN TESTING

GEORGE G. STILWELL

DURING the past few decades the death rate from tuberculosis has dropped tremendously. The decline in morbidity and the great decrease in the number of cases of open tuberculosis are phenomena which are well known. It is not such common knowledge that these changes have altered to a certain extent the role of the tuberculin test as a diagnostic aid. It is the purpose of this presentation to review some of the basic facts regarding tuberculin tests and their interpretation, and to emphasize the increasing importance of the test in adults.

TYPES OF TUBERCULIN

Koch made the discovery that the fluid medium used for growing *Mycobacterium tuberculosis* was toxic when administered to a tuberculous person. He determined that the active substance in this fluid was protein in nature. The term "tuberculin" is used to designate any material which contains this tuberculoprotein or its degradation products and which is capable of producing the reactions of hypersensitivity in a person who has become sensitized as a result of past or present tuberculous infection. Many different preparations have been so designated and two of these have attained the greatest acceptance.

The first of these is old tuberculin, commonly termed "OT." This is simply the fluid medium in which tubercle bacilli have been grown. It is sterilized by heat, filtered and then concentrated to a tenth of its original volume.

Seibert later found that tuberculin contained a protein of low molecular weight which produced a highly toxic reaction when administered to tuberculous persons. The effect of this protein created upon hypersensitive tissues was characteristic of those produced by ordinary tuberculin. This is the second main type of tuberculin and is commonly termed "purified protein derivative" and commonly "PPD." It is a highly potent purified tuberculin preparation from cultures of tubercle bacilli on nutrient media.

precipitation with trichloroacetic acid. Since the antigenicity of this material has been reduced by heating, it may be safely used for repeated testing in the same case. The purified protein derivative which is now available commercially is approximately 200 times as effective, by weight, as old tuberculin. It is much less variable in potency, does not tend to produce false positive reactions upon repeated testing, and is undoubtedly the tuberculin of choice.

METHODS OF TUBERCULIN TESTING

Pirquet in 1907 described the cutaneous scratch tuberculin test and applied the name "allergy" to the properties which were responsible for the manifestations of the tuberculin reaction. In 1908, Mantoux recommended the use of the intracutaneous test, which is at present the most widely used technic. The Vollmer patch test has attained some favor in recent years, particularly in pediatric practice where it has the advantage of avoiding use of a needle. One disadvantage of this test is the possibility of faulty contact of the tuberculin impregnated paper with the skin.

The initial dose of old tuberculin for the Mantoux intracutaneous test is usually 0.1 cc. of a 1:10,000 dilution. This amount contains 0.01 mg. of old tuberculin. If negative reactions ensue, the dose is increased tenfold on two occasions until 1.0 mg. is given. If no reaction is produced with this dose, a dose of 5 mg. and 10 mg. may be administered. Under ideal conditions, the reaction should not be classified as genuinely negative unless the intradermal injection of 10 mg. of old tuberculin fails to produce a characteristic area of hyperemia around the site of injection. Practically, it is seldom that such a series of tests is feasible. In large scale testing, an initial dose of 0.01 mg. is used, if the reaction to this dose is negative, another test is performed by injecting 1.0 mg. of old tuberculin. This method will prove satisfactory in most cases, but the injection of 10 mg. of old tuberculin will produce a positive reaction in a small number of cases in which the injection of 1.0 mg. will fail to do so.

The initial dose (first-strength dose) of commercial purified protein derivative is 0.00002 mg. If the injection of this dose fails to produce a positive reaction, one should inject a dose of

0.005 mg (second strength dose), which is 250 times as large as the initial dose. False positive, nonspecific reactions may occur with the second-strength dose. In an effort to obtain as much information as possible with a minimal amount of time and testing it has been proposed that a single, compromise dose of tuberculin be used. Furcolow, Hewell, Nelson and Palmer of the United States Public Health Service used purified protein derivative in a series of quantitative tests and found that the most efficient dose for a single test was 0.0001 mg, which is 5 times as large as the standard first-strength dose. The use of this single test will disclose tuberculosis in 95 per cent of cases in which significant disease is present. This single-dose tuberculin test has been employed for the past two years at the Clinic on patients who were 16 years of age or older, and it has given satisfactory results. Occasional, rather severe local reactions are encountered but the method appears to be quite safe if it is applied to population groups in which the incidence of tuberculosis is fairly low. This initial dose would not be advised in surveys of groups in lower economic levels, in which a large percentage of persons have been exposed to tuberculosis. It should be used with caution or not at all in cases in which the presence of ocular tuberculosis or tuberculosis of the bones, skin or lymph nodes is suspected. Weaker doses of tuberculin should be used in the initial testing in such cases.

Because of the lower degree of tuberculin sensitivity usually encountered among children, particularly those from population groups in the better economic levels, it is considered safe to use a stronger dose of tuberculin in the initial test on young persons. For some years, an initial dose of 0.0002 mg of purified protein derivative has been used at the Clinic for children 15 years of age or younger. This dose contains 10 times as much purified protein derivative as the standard first strength dose. Even with the use of this stronger dose we very rarely encounter four plus reactions in these younger patients.

CRITERIA OF POSITIVE TUBERCULIN REACTIONS

Interpretation of tuberculin surveys reported in the literature has been rendered confusing because of lack of uniformity.

in classifying the skin reactions. Some investigators have considered as positive only those reactions in which there is an area of edema 10 mm or more in width. Others have designated as positive any reaction characterized by palpable induration and erythema. One author has described six different degrees of sensitivity but has not adequately delineated the lower limit of a positive reaction. Some physicians accept as an indication of a positive reaction the smallest papule that can be clearly distinguished from needle trauma or other reactions caused by nonspecific factors.

It is urged that a uniform interpretation of tuberculin reactions be used. Such a scheme has been suggested by the National Tuberculosis Association. The criteria of positive reactions according to this classification are as follows:

Doubtful (\pm) —Slight erythema and a trace of edema which measures less than 5 mm in diameter

One plus (+) —Erythema and edema which measures 5 to 10 mm in diameter

Two plus (++) —Erythema and edema which measures 10 to 20 mm in diameter

Three plus (+++) —Marked erythema and edema which is more than 20 mm in diameter

Four plus (++++) —Erythema, edema and central necrosis.

Edema is more important than erythema, and if edema is not present the reaction is considered negative. It is usually recommended that the reaction be inspected forty-eight hours after the test dose is injected. This appears to be the optimal time for observing the reaction, but in an occasional case the reaction is entirely negative at forty-eight hours but becomes strongly positive a day or so later.

DEVELOPMENT AND VARIATIONS OF THE TUBERCULIN REACTION

It usually requires from three weeks to three months after tuberculous infection for the tissues of an infected person to become sufficiently sensitized to respond with a measurable reaction to injection of tuberculin. The time of appearance of this allergic phase depends on several factors, among which are the individual response to infection, the size of the in-

fecting dose and the speed with which healing occurs. The reaction rapidly becomes strongly positive and remains so while the lesion undergoes encapsulation. With death of the organisms and gradual removal of the antigenic substances, the extent of the reaction slowly decreases, although fairly rapid fluctuations in intensity may be seen. Any sudden liberation of excess antigen usually decreases the severity of the reaction. This may occur when many tubercle bacilli and much caseous material suddenly gain access to the blood stream from rupture of a caseous focus into a vessel. It also occurs when large amounts of tuberculoprotein enter the lung when a caseous focus erodes into a bronchus, or when a subpleural focus discharges into the pleural cavity. In cases of far advanced and rapidly progressive tuberculosis, the presence of a great excess of antigen often decreases the severity of the reaction and may even eliminate it entirely by producing an anergic phase in the patient.

Temporary depression of the cutaneous sensitivity of a tuberculous patient may be encountered in pregnancy or during the course of associated diseases such as influenza, undulant fever and measles. This diminution in the tuberculin reaction is nonspecific in nature and is accompanied by a general decrease in skin reactions to many other agents. It is apparently caused by alteration in the response of the cutaneous capillaries. Other conditions associated with the possibility of false negative tuberculin reactions are cachectic states and hypothyroidism.

Another important factor to be considered in tuberculin testing is the length of time during which a person will continue to display a positive reaction in the absence of further antigenic stimulation from tuberculoprotein. The interval between death of tubercle bacilli and complete cessation of skin sensitization varies from two to many years. This period depends on many considerations such as initial virulence of the bacilli, size of the lesion, host resistance and subsequent exposure to other patients who have open tuberculosis.

CLINICAL IMPLICATIONS OF TUBERCULIN TESTING

The tuberculin test has played an important part in the program of immunization against tuberculosis by BCG vacci-

nation At present, this program is coming to the fore in this country because of the great increase in the use of this immunizing procedure now being planned by various agencies concerned with the control of tuberculosis Selection of patients for vaccination is made by means of the tuberculin test, as only those who display a negative skin reaction should be considered as candidates for inoculation with BCG (*Calmette-Guérin bacilli*) Tuberculin testing is an important feature of the study of those persons who have been vaccinated with BCG, because the reversal of the skin reaction from negative to positive after inoculation is the only immediate and tangible evidence that any change in the immune mechanism of the patient has occurred Much can probably be learned concerning the mechanism of the development and persistence of skin sensitization after tuberculous infection by a study of vaccinated persons because inoculation with BCG produces a minimal and most benign tuberculous disease The *Calmette-Guérin bacilli* soon disappear from the lesion and undoubtedly die in a short time Thus the skin reactions which follow BCG vaccination should be similar to those seen after a natural infection which is caused by a small initial dose of avirulent tubercle bacilli and is accompanied by rapid healing

In cases of healed tuberculosis there is a definite tendency for cutaneous sensitivity to disappear Thus a negative tuberculin reaction does not mean that the person who fails to react has never had tuberculosis The frequency with which tuberculous patients undergo reversal of the tuberculin reaction varies considerably but it is probable that this change will become more common as the years pass There is a definite relationship between the frequency of reversal of tuberculin reactions and the degree of sensitivity exhibited by the patient on his original test

Two thousand four hundred and ninety persons who previously had reacted positively to the intradermal injection of old tuberculin or purified protein derivative were observed for from five to fifteen years by Dahlstrom Of these 2,490 persons, 276 (11.1 per cent) subsequently failed to react positively to the intradermal injection of old tuberculin or purified protein derivative This reversal of the reaction occurred much more

frequently in cases in which the sensitivity to the initial injection was low. A subsequent reversal of the reaction was observed in only 4 of the 1,090 cases in which intradermal injection of 0.00002 mg. of purified protein derivative or 0.01 mg. of old tuberculin produced a reaction that was classified as 3 plus. On the other hand, a reversal occurred in 131 (70.8 per cent) of the cases in which the intradermal injection of 0.005 mg. of purified protein derivative or 0.1 or 1.0 mg. of the old tuberculin produced a reaction that was classified as 1 plus. In most of the cases in which there was a reversal of the reaction from positive to negative, the patients were children, a similar reversal of the reaction was observed rarely among adults.

Röntgenologic examination of the thorax frequently discloses evidence of old tuberculosis in cases in which the reaction to tuberculin is negative. This finding has been cited to show how frequently a loss of sensitivity to the injection of old tuberculin or purified protein derivative may occur. Surveys show that roentgenologic examination of the thorax may disclose some evidence of tuberculosis in as many as 25 per cent of cases in which the intradermal injection of as much as 1.0 mg. of old tuberculin fails to produce a positive reaction. These figures must now be interpreted in the light of newer knowledge. In most of these cases, the only evidence of tuberculosis was the presence of calcified areas in roentgenograms of the thorax. Since the advent of surveys in which the histoplasmin test is used, it has been found that this test frequently is positive in cases of calcified lesions of the thorax in which the tuberculin reaction is negative. It may well be that the calcified lesions in such cases are not the result of previous tuberculous infection.

The occurrence of these changes in tuberculin sensitivity is an important point in the clinical interpretation of negative reactions to tuberculin. Enough clinical evidence has now been accumulated to warrant the assumption that although a tuberculous patient who has conquered his infection may completely lose his cutaneous sensitization, he still will retain his acquired resistance to further infection. Immunity against tuberculosis in such a case is entirely different from the immu-

ity of a person who has never been infected and who reacts negatively to the intradermal injection of old tuberculin or purified protein derivative. Further evidence to uphold this belief is seen in the fact that experimentally infected animals that have lost their cutaneous sensitization still demonstrate a high degree of resistance to further infection that was given them by the original disease. In some institutions, only those student nurses who react positively to the injection of tuberculin are chosen for training in a tuberculous unit, on the assumption that a past infection which has completely healed and has resulted in a cutaneous hypersensitivity will provide the student with considerable immunity against the disease. Emphasis should be placed on the point that a negative reaction to tuberculin does not always mean that the patient has not had tuberculosis and that the person has no immunity against the disease.

In the early part of this century when most adults were at one time or another infected with tuberculosis, and when most people came into contact with many patients who had open tuberculosis, the incidence of positive reactions to tuberculin among adults was very high. This led to the conclusion that it was worthless to use the tuberculin test as a diagnostic aid in cases in which adults had disease of the thorax, and the tuberculin test was thought to be of value only as an aid in determining the occurrence of infection in children. With the great decrease in number of cases of open tuberculosis there has been a concomitant decrease in the occurrence of positive reactions in the adult population, therefore, statistical conclusions drawn from tuberculin surveys made 20 or 30 years ago are no longer valid.

It seems, therefore, urgently indicated at this time to undertake new country-wide surveys of varied adult groups to determine the modern incidence of sensitivity to tuberculin. Rich expressed the opinion that more needed information can be gained at present from adult surveys than from surveys carried out on children, because children acquire their tuberculosis for the most part from adults.

It is evident, therefore, that in the case of adults, the tuberculin test is becoming an important aid in general

diagnosis, particularly when one is dealing with puzzling diseases of the thorax. The importance of this test will increase in future years as the incidence of tuberculosis continues to decrease. No longer valid is the assumption by the clinician that the results of tuberculin testing of adults are meaningless because of the preponderance of positive reactions among adults in previous decades. The tuberculin test should be applied as one of the first diagnostic procedures in any case in which the clinical features might possibly be due to tuberculosis.

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RECENT TRENDS IN THE TREATMENT OF INFECTIOUS DISEASES

DONALD R. NICHOLS

THE many advances made in the field of antibiotic and chemical therapy in the past few years have increased rather than decreased the importance of the accurate diagnosis of infectious diseases. An accurate clinical and bacteriologic diagnosis is essential if the most effective method of treatment is to be employed. Each of the antibacterial agents is effective against certain specific diseases, but entirely ineffective against others. When an antibiotic drug is used in diseases in which it is not indicated, there is a definite risk that the patient may be needlessly sensitized to the drug and also that resistant bacteria may be permitted to develop. Combinations of chemotherapeutic agents are definitely indicated in certain infections. However, in the treatment of most diseases combinations of antibacterial agents are to be avoided. Physicians therefore, are becoming increasingly aware of the importance of establishing an accurate diagnosis rather than of using the "trial-and-error" method of treatment.

During the past two years a few new antibiotic agents have been described, but none has come into general use. Most of these new agents either have been too toxic for systemic administration or have not been found sufficiently active to justify further investigation. Some encouraging experimental results have been obtained with chloromycetin, polymyxin and aerosporin. Bacitracin is being given a rather extensive clinical trial. Its activity appears to be chiefly against certain gram positive organisms. Satisfactory clinical results have been reported from the local use of the material in cellulitis caused by hemolytic streptococci and in some staphylococcal infections.¹ The nephrotoxic reactions which bacitracin produces have limited its systemic use thus far.

NEW PREPARATIONS AND METHODS OF ADMINISTRATION

Most of the recent clinical investigative work has been directed toward improving the methods of using the chemo-

therapeutic agents which are available at present. An attempt to review all of this investigative work is beyond the scope of this paper. However, a few of the recent observations are of considerable interest to the clinician.

Procaine Penicillin G.—Procaine penicillin G is a satisfactory preparation for the prolongation of an effective concentration of penicillin in the blood.⁵ Numerous preparations and methods of administration have been employed in the past in an effort to prolong the action of penicillin. Procaine penicillin G appears to achieve the desired effect much more satisfactorily than previously described preparations or methods. Procaine penicillin G is a crystalline, nonpyrogenic substance which is prepared by combining 1 molecule of procaine base with 1 molecule of penicillin. This salt is relatively insoluble in water. Therefore, procaine penicillin G is usually suspended in various types of oil. At present sesame oil appears to be the most satisfactory oil for this purpose. Each cubic centimeter of the suspension contains 300,000 units of penicillin and 125 mg. of procaine. The material can be injected through a no. 19 or 20 needle. It is important to shake the solution vigorously, and often it is advisable to warm the ampule slightly in the hand before injection. An effective therapeutic concentration of penicillin in the blood is usually obtained for at least twenty-four hours when 1 cc. of procaine penicillin G is injected intramuscularly. To date, the material appears to be entirely safe and has not given evidence of serious toxic effects. The incidence of reactions appears to be minimal. However, the fact that small deposits of oil often persist for months after the intramuscular injection of substances suspended in oil must not be overlooked. Therefore, the frequent repeated use of suspensions in oil in the same region does not seem advisable. Clinical results of use of procaine penicillin G in the treatment of infections appear to be the same as those which would be expected when any other form of adequate penicillin therapy is employed.

Caronamide (4'-Carboxyphenylmethanesulfonamide¹).—In most types of infections caused by organisms which are sensitive to penicillin high concentrations of penicillin in the body fluids are not necessary. However, in certain

infections, for example, subacute bacterial endocarditis and actinomycosis, high concentrations of penicillin in the body fluids appear to be necessary in order to obtain satisfactory results. The continuous intravenous drip method of administration still appears to be the most effective and safest method of achieving these very high concentrations. At times, even this method of administration fails to provide a sufficiently high concentration, and methods of interfering with the excretion of penicillin through the urinary tract must be considered. Use of para-aminohippuric acid and iodopyracet injection (diodrast) has not proved practical from the clinical standpoint. The use of caronamide probably is the best method of impairing the renal excretion of penicillin which is available at present. The results of giving 2 gm. of caronamide every three hours were disappointing and no appreciable augmentation of the level of penicillin in the blood was obtained. However, it appears that a dosage of 4 gm. of caronamide every four hours significantly increases the concentrations of penicillin.¹ This dosage often produces signs of renal irritation while the drug is being given, therefore, although no permanent renal damage has been reported, the drug probably should be used only when specifically indicated.

Combinations of Sulfonamide Compounds—The studies of Lehr in 1946 suggested the possibility that the frequency of renal complications caused by the sulfonamide drugs could be reduced by use of a combination of these drugs. He reported that the various sulfonamide drugs, when present simultaneously in the same solution in the free form, were soluble to the extent of their separate solubilities. Thus, a saturated solution of sulfadiazine could be almost completely saturated with sulfathiazole. In studies on animals it was found that the precipitation of sulfonamide crystals in the kidney was significantly less when the mixture was used. The therapeutic effectiveness of the individual drugs appeared to be maintained. Clinical results obtained when combinations of the sulfonamide compounds are used appear to be about the same as would be expected when one of the sulfonamides is used alone. Most investigators have reported that renal complications are reduced when two or more of

the sulfonamide compounds are used simultaneously.³ However, a disquieting observation has been made by Zeller and his co-workers. They reported a significantly higher incidence of allergic reactions, that is, fever, rash and conjunctivitis, in patients who have received combinations of sulfonamide compounds. If this observation is borne out by further experience, the disadvantages of combinations of sulfonamide compounds may well outweigh the advantages.

ADVANCES IN THE TREATMENT OF CERTAIN SPECIFIC DISEASES

Definite advances have been made in the management of certain specific infectious diseases. Encouraging results have been obtained in several diseases for which there previously has been no effective form of treatment.

Brucellosis—One of the most recent advances in the management of infectious diseases has occurred in the treatment of brucellosis. In February, 1947, Pulaski and Amspacher reported the successful cure of 2 patients who had acute brucellosis by treatment with a combination of streptomycin and sulfadiazine. In October, 1947, Spink and his co-workers reported their extensive experience with different forms of treatment for brucellosis. From their laboratory and clinical observations, they concluded that the combined use of streptomycin and sulfadiazine in the treatment of patients with acute and chronic brucellosis yielded more satisfactory results than had previously been obtained by other methods of treatment.

Since learning of the favorable results obtained by Pulaski and Amspacher, my associates and I have treated 12 patients who had brucellosis with a combination of sulfadiazine and streptomycin. The response of most of these patients to this form of treatment has been excellent. In 1 case positive blood cultures recurred. The others have remained well. The optimal dosage for this combination of drugs has not been determined with certainty. However, the following schedule has given satisfactory results in most cases. A dose of 0.5 gm. of streptomycin is administered intramuscularly every six hours for seven to ten days. Sulfadiazine is administered simultaneously by mouth in a dose of 4 gm. initially and then 1 gm. every four hours thereafter for two or three weeks.

Plague —In 1944 Heilman demonstrated the effectiveness of streptomycin against *Pasteurella pestis* in vitro.¹² Karamchandi and Rao recently reported the favorable response to streptomycin of patients suffering from infections caused by this organism. It is sincerely to be hoped that further clinical studies will tend to be as favorable. Plague is a world-wide disease of serious proportions and to date there has been no satisfactory treatment.

Rocky Mountain Spotted Fever —Preliminary studies by Flinn and his co-workers have tended to confirm previous laboratory findings that para-aminobenzoic acid is an effective agent in the treatment of Rocky Mountain spotted fever. A dosage of para aminobenzoic acid sufficient to produce a level of 30 to 60 mg per 100 cc. of blood has been suggested. The duration of the disease appears to be shortened by this method of therapy. However, further clinical experience will be necessary before a final evaluation of this form of treatment of certain rickettsial diseases can be made.

Actinomycosis —Because of the chronic nature of actinomycosis and because of the tendency of the infection to relapse long after apparent cure, the evaluation of treatment for actinomycosis has been difficult. In 1943 Florey and Florey reported the results of treatment with penicillin of 2 patients who had actinomycosis. In these patients penicillin appeared to have no effect on the infection. However, reports published since then on the use of penicillin in the treatment of actinomycosis have been more encouraging. The results obtained in patients whom we have treated appear to indicate that penicillin when given in large doses, is an effective agent in the treatment of actinomycosis, its effectiveness varies somewhat with the location of the lesion.⁹

Forty-six patients who had actinomycosis have been treated with penicillin under our supervision and have been followed for from one to five years. Of 26 patients who had cervicofacial actinomycosis, 24 had excellent results. These results were obtained after an average period of treatment of less than two months, a period significantly less than the usual length of time required to obtain comparable results when penicillin was not used. Of 9 patients who had pulmonary

actinomycosis, 5 recovered Of 8 patients who had abdominal actinomycosis, 6 recovered All 3 patients who had pelvic actinomycosis recovered All strains of *Actinomyces bovis* cultured from these patients were sensitive to penicillin in vitro

Cervicofacial actinomycosis has responded well to several methods of treatment Prolonged surgical drainage, roentgen therapy and administration of iodides and some of the sulfonamide compounds have proved of value in the treatment of actinomycosis when it involves the neck or face However, penicillin appears to have shortened the duration of the infection and the period of treatment

Pulmonary actinomycosis has nearly always been a progressive and fatal disease The usual methods of treatment have been ineffective in most cases Therefore, recovery of 5 of the 9 patients who had pulmonary actinomycosis is most encouraging

Abdominal actinomycosis has always been a serious disease Good results have been obtained in occasional cases by several methods of treatment However, the percentage of patients who recovered has never been high, and the prognosis has been poor Seventy-five per cent of our patients with abdominal actinomycosis who received penicillin recovered It appears, therefore, that penicillin is an effective agent in the treatment of abdominal actinomycosis

The prognosis when actinomycosis involves the pelvic organs has been extremely poor, and few recoveries have ever been reported Therefore, the recovery after treatment with penicillin of 3 women who had actinomycosis involving the pelvic viscera seems particularly significant

In the treatment of all types of actinomycosis a dosage of at least 500,000 units of penicillin daily, administered intramuscularly or intravenously, for six weeks appears to achieve the best results Adequate drainage is indicated if abscesses are present, and excision of diseased tissue may be advisable in some instances It seems possible that even better results can be achieved in the future if administration of adequate amounts of penicillin is combined with the use of sulfonamide compounds, streptomycin or roentgen therapy

SUMMARY

The many advances made in the field of antibiotic and chemical therapy in the past few years have increased rather than decreased the importance of the accurate diagnosis of infectious diseases. When an antibiotic drug is used in diseases in which it is not indicated, there is a definite risk that the patient may be needlessly sensitized to the drug and also that resistant bacteria may be permitted to develop.

Procaine penicillin G in oil is a satisfactory preparation for prolonging the effective concentration of penicillin in the blood. When 1 cc. of procaine penicillin G is injected intramuscularly, an effective therapeutic concentration of penicillin is usually obtained in the blood for at least twenty-four hours.

The use of caronamide probably is the best method of impairing the renal excretion of penicillin. While caronamide is being given, signs of renal irritation often appear. The drug, therefore, should probably be used only in certain selected cases.

Combinations of two or more sulfonamides maintain the therapeutic effectiveness of the individual drugs and appear to diminish the incidence of renal complications. However, if use of a combination of sulfonamide compounds produces a higher incidence of allergic reactions, the advisability of such a combination is questionable.

Definite advances have been made in the management of certain specific infectious diseases. The combined use of streptomycin and sulfadiazine in the treatment of patients who have acute or chronic brucellosis appears to yield more satisfactory results than have been obtained by other methods of treatment. Clinical reports on the effective use of streptomycin in the treatment of plague and of para-aminobenzoic acid in the treatment of Rocky Mountain spotted fever tend to confirm laboratory observations. Penicillin has been shown to be an effective agent in the treatment of actinomycosis and a useful adjunct to other forms of therapy of this disease.

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PRESENT-DAY CONCEPTS OF THERAPY IN PERNICIOUS ANEMIA: A REVIEW

JOHN E STEVENS AND BYRON E HALL

WITHIN the last two decades, progress in the treatment of pernicious anemia has represented one of the foremost advances of medicine. Minot and Murphy¹⁰ in 1926 demonstrated the value of liver therapy in this disease, and in recent years "folic acid"¹¹ as a therapeutic agent has been widely publicized. An evaluation of therapy as it has progressed during this period is therefore, pertinent. It is the purpose of this paper to review briefly the advances in treatment and to present the physiologic basis for therapy.

It is not within the scope of this discussion to deal with the various general physiologic changes that occur with pernicious anemia, although all will agree that any attempt at discussion of therapy necessarily entails a basic understanding of the pathologic physiology.

HISTORICAL DATA

Thomas Addison in 1849 and again in 1855 described "a very remarkable form of general anemia, occurring without any discoverable cause whatever." It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. After a sickness of, perhaps several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect."

In 1872 Biermer suggested that Addison's name be given this anemia, but it was he who described it as a "progressive pernicious anemia." It was pernicious in that, in spite of all treatment, sooner or later the patients succumbed. In recognition of these two early observers the term, "Addison-Biermer anemia," is often heard.

DEFINITION, BASIC PATHOLOGIC PHYSIOLOGY AND THE ROLE OF LIVER IN THERAPY

Classical Addisonian pernicious anemia, as understood today, is a deficiency disease due to the lack of a specific

substance necessary for the growth and development of erythrocytes. This substance, the exact nature of which is unknown, is found especially in the liver and is known as the erythrocyte maturation factor (E M F) or the antianemic principle (A A P). It is as specific in the therapy of pernicious anemia as insulin is in diabetes mellitus.³⁴

The diagnostic triad of progressive changes in the digestive, blood and nervous systems indicates that long-continued deficiency of this specific substance must be viewed as provocative of a symptom complex. The disease is not just an anemia, per se, of macrocytic hyperchromic type, but is characterized also by pathologic changes in the tongue, gastric mucosa, bone marrow and nervous system.

The disease occurs only in adults and is characterized by remissions. In addition, signs and symptoms which one may expect with any severe anemia, such as weakness, dyspnea, dizziness, sore, smooth tongue, achlorhydria and evidences of central nervous system involvement including sclerosis, peripheral neuritis and psychosis, also may be observed.

To understand therapy of this disease, it is important that the steps in the formation and utilization of the antianemic principle be reviewed. It is now generally agreed that at least five steps are involved in the elaboration and use of the substance or substances necessary for normal maturation of erythrocytes and for the prevention of the symptom complex mentioned previously. These steps are as follows:³⁴

- 1 Provision of an extrinsic factor in the food.
- 2 Secretion into the gastric juice of an intrinsic factor contained in the gastric mucosa.
- 3 An interaction of the extrinsic and intrinsic factors in the gastro-intestinal tract to form an antianemic substance which is absorbed by the intestine.
- 4 The storage of the antianemic substance by the liver, and perhaps its further modification in that organ.
- 5 The release of the antianemic principle to the hemopoietic tissues and its utilization by the bone marrow in normal erythropoiesis.

Achlorhydria was recognized early as a diagnostic feature of pernicious anemia. It was believed that achlorhydria or its

effect on intestinal flora might be an etiologic factor. Every organism that inhabits the lumen of the gut was suspected, at one time or another, of causing the disease.²¹ Hemolytic toxins absorbed from the gastro-intestinal tract, gastro-intestinal toxemia resulting from *Escherichia coli*, and infections with *Clostridium perfringens* (welchii) and *Streptococcus longus* were indicated as etiologic factors.

Treatments during this period were as numerous and varied as the many theories advanced for the genesis of this disease. Iron, hydrochloric acid, arsenic, gentian violet and acriviolet,²² removal of infection and drainage of the intestinal tract were tried. Any treatment at times seemed to produce a remission, and transfusions were often used. Dependence could not be placed on any form of treatment, however, and anemia or intercurrent disease was a common cause of death.²³

In 1926 Minot and Murphy²⁴ announced that they had produced rapid remission in the anemia and symptomatic improvement in 45 patients with Addisonian pernicious anemia by feeding them a diet rich in liver. This discovery marked the beginning of our present concept of therapy in this disease and has withstood the test of time. In recognition of this important work, these two investigators along with George H. Whipple were awarded the Nobel Prize in medicine and physiology in 1934.²⁵

Castle's observations²⁶ formed the next important step in the understanding of the pathologic physiology of this disease. He found that if ground beef muscle were fed to a normal person and, after partial digestion, the contents of the stomach were recovered and fed to a person with pernicious anemia, marked symptomatic and hematologic improvement was seen. It was further shown that normal human gastric juice or beef muscle alone was ineffective in producing a favorable response in these patients. Nor was a favorable response obtained if beef muscle were treated with gastric juice obtained from a person suffering from pernicious anemia and fed to another such patient.

It was believed then for the first time that a definite relationship between the function of the stomach and the function of the bone marrow existed. In patients having pernicious

anemia it was apparent that some constituent of normal gastric secretion was lacking and that because of this deficiency normal blood formation was interfered with. While achlorhydria was invariably found in these patients, neither hydrochloric acid nor any of the other constituents of normal gastric juice, such as pepsin, rennin or lipase, was found to be effective in causing a hematologic remission.

This unknown substance that was lacking in the gastric juice of these patients, yet present in normal people, Castle called the *intrinsic* factor. An *extrinsic* factor, or food factor, was found in beef muscle and was thought to be a protein. Interaction between the two factors produced the antianemic substance which was absorbed from the gastro-intestinal tract and stored in the liver, kidney and other body tissues. The erythrocyte maturation factor was then released to the bone marrow and other hematopoietic tissues for erythropoiesis.

The lack of intrinsic factor, the less probable lack of extrinsic factor found in various foods or the poor absorption, from the intestinal tract, of the antianemic substance formed by the interaction of the two factors all are theoretical causes for the development of pernicious anemia.¹²⁻¹⁶ The role played by achlorhydria, while not fully explained, certainly cannot be thought of as an essential factor in the pathogenesis of this disease. Many persons having achlorhydria never experience pernicious anemia, and those patients being treated successfully for their anemia show no return of the acid in their gastric juice.

The fact that liver, rich in stored antianemic principle, could produce remissions in these patients was added proof that Castle's hypothesis was correct. From that time forward, treatment of pernicious anemia was no longer on empirical ground, but on a sound physiologic basis.

DESICCATED STOMACH AS A THERAPEUTIC AGENT

When it became apparent that the basic deficiency in pernicious anemia was lack of intrinsic factor which, in turn, gave rise to the inability to form the erythrocyte maturing factor, it was logical to turn attention to the intrinsic factor in the standpoint of therapy. Sturgis and Isaacs were the

first to utilize desiccated whole hog stomach in therapy. Their preparation was prepared so that 30 gm of the dried substance was equivalent to 190 gm of the fresh stomach. Further refinement after removal of fat made 30 gm of dried substance equivalent to 218 gm of fresh tissue. Three patients were treated with daily doses ranging from 15 to 30 gm. In all 3, prompt hematologic remissions comparable to those achieved by the use of liver occurred. In fact, these original investigators suggested that gastric tissue was more active, per gram, than was liver. While this observation has not been substantiated, gastric tissue is equally as effective as, but not superior to, liver.

The rationale of the use of stomach preparations is that the mucosa and wall of the stomach represent both intrinsic and extrinsic factors respectively. Since patients suffering from pernicious anemia have lost, or never have had, the ability to secrete intrinsic factor with the power to produce, from the food, the material necessary for blood maturation, the use of gastric tissue was another means of supplying their needs.

Administration of raw hog stomach was found to give results similar to those obtained from use of the dried preparation; however, larger amounts were necessary. Whether or not preparations were made from the gastric mucosa or gastric wall in the fundus or pylorus seemed to make little difference. Remissions were induced and maintained satisfactorily. The picture of blood regeneration was similar, and apparently equivalent, to that in patients undergoing liver therapy.^{11,22} The increase in appetite and general well-being was attributed to the decrease in blood sugar and to increased metabolic activity of either the bone marrow or the immature erythrocytes or both, when remission began. In relapse, the blood sugar level was usually within the upper limits of normal and reached values as low as 61 mg per 100 cc during early remission when the percentage of reticulated erythrocytes rose. These values were found to return to more nearly normal levels with improvement.²²

Finally, a preparation consisting of liver that has been extracted of its gastric tissue was later used. The effect exerted by the stimulation in producing a remission seemed to be

greater than the sum of the effects of the two component materials ²³ It has proved to be one of the most potent anti-anemic preparations available for oral use

Bethell and Goldhamer⁵ were among the first to compare the efficacy of ventriculin and extracts of liver administered intravenously, using maximal reticulocyte values as an index While desiccated stomach gave a definitely greater response than did extracts of liver when administered orally, it was found that a preparation made from liver and given *intravenously* led to a reticulocyte response which was considerably greater than that obtained from any preparation given *orally*. The significant difference in degrees of response was concluded to be due to the rate at which the effective material reached the bone marrow and not due to the total amount administered to the patient

LIVER THERAPY

General Considerations—Since Minot and Murphy's memorable discovery that a diet rich in liver produces and maintains remissions in patients with pernicious anemia, many important refinements in liver therapy have been made

It was found that an extract made from whole liver and administered parenterally acted just as well as did fresh liver given orally and, in addition, allowed the patient more dietary freedom Extracts for oral administration are still widely used by many physicians, although forms for parenteral use have been perfected to the point that injections every two to four weeks of a potent extract will maintain the blood in a normal condition and will prevent the development of neurologic lesions

Nothing is more dramatic in medicine than the effect of liver treatment on patients with pernicious anemia ³⁵ In brilliance of results it ranks with the use of insulin in diabetes and the sulfonamides and antibiotics in infections

As a result of liver therapy the type of patient so aptly described by Addison can be returned rapidly to the picture of health His glossitis and gastro-intestinal symptoms disappear rapidly His neurologic signs and symptoms improve, or at least do not progress, and at times disappear entirely

It is the latter point that makes this form of therapy more desirable than the current use of "folic acid," as will be pointed out later

While no single substance in liver or liver extracts responsible for the beneficial effect has been isolated, extracts of liver are now fairly well standardized and their potency controlled. Refinement has been perfected to the point that a maximal response is obtained with a minimum of inconvenience and discomfort to the patient

In spite of the progress made in refining preparations of liver, the warning given by Minot⁴⁰ remains applicable "The grave error in treatment is to prescribe too little liver extract or potent substitute. Where there is doubt, more rather than less should be given. It is essential that the individual receive into his body indefinitely and with regularity enough potent material for his given case."

There is no strict regimen for therapy of pernicious anemia with preparations of liver. Any effort to standardize maintenance therapy should be condemned,⁴² for the patient often will not be maintained adequately with routine treatment. By giving large doses in the early stage of treatment and then by careful observation of neurologic disturbances and studies of the blood to determine the individual maintenance dose required, one is not likely to be disappointed by a poor response to therapy.

An excellent illustration of the need for individualized therapy is the case recently reported⁴⁷ in which a patient was observed over a period of twenty years who required, in addition to one to two injections of liver extract per week, an average of one half pound of raw liver per day. If only injections were given, the patient experienced headache, backache, ataxia and incontinence of urine which subsided when large quantities of liver were given orally. This case serves to illustrate that in rare instances enormous doses of raw liver, in addition to extracts of liver administered parenterally, may be required to control the disease.

Types of Liver Preparations Available—The type of liver preparation to use is again an individual factor. Except for the differences to be enumerated, it is wiser to become

familiar with one or two preparations and to use them exclusively than to change from one to another indiscriminately

The oral route of administration has several disadvantages. The quantity of potent material absorbed in the gastro-intestinal tract and the amount lost in the stools may vary from time to time in the same patient or may vary from patient to patient, the physician may have difficulty in maintaining adequate control of the disease in patients who take extract irregularly and the cost of adequate oral therapy to the patient may be considerably higher than the cost of parenteral administration.

Preparations for parenteral use may be obtained in crude or refined form. Crude extracts once were believed to be more efficacious than purified preparations, especially in patients with neurologic manifestations. However, there is no evidence to show that this is true.⁵² Crude preparations are more expensive to the patient than the highly refined products, because greater amounts and more frequent injections are required to control the disease. Some preparations actually are dilutions of the refined products and contain greater amounts of inert solids. Because of this, they are irritating and often cause discomfort.

The refined preparations are more highly concentrated and offer a maximal response with a minimum of expense and inconvenience to the patient. Neurologic disturbances respond more rapidly to the use of these preparations, provided the amount is adequate and the duration of treatment is sufficient. Perhaps it is trite to say that once liver therapy is begun, it must be maintained indefinitely. In this respect, it is akin to insulin in the maintenance of the diabetic.

Prognosis with Liver Therapy.—The results of liver therapy in prolonging the life span of those with addisonian anemia offer the best argument for the use of this form of treatment. Studies of data⁶¹ on mortality in a Canadian group showed that eight years after the discovery of the effects of liver therapy, deaths attributed to this disease were only 46 per cent as numerous as usually obtained in the period prior to the use of liver

It has been estimated that in the United States alone there were annually 10 000 deaths prior to the introduction of liver therapy. At present there are 100,000 persons with this disease who would not be alive today except for liver or its extracts.¹²

Allergic Reactions to Liver—One occasionally sees patients who are hypersensitive to extracts of liver, but few reports on this subject have been published. Kaufman and associates gave an excellent bibliography on the 50 cases of sensitivity to injections of liver extract for the twelve year period ending in 1943. They reported 11 additional cases, while Schwartz and Legere in a recent study found that 68 of 396 patients (17 per cent) had varying degrees of sensitivity. While the physician should be aware of the possibility of sensitivity, he should not let such awareness deter him from the use of this valuable form of therapy, since sensitivity is of comparatively rare occurrence and means are available to combat it.

The clinical picture of hypersensitivity develops after a patient has had several injections of liver extract. Then, after an injection of the extract, generalized or localized itching occurs. In addition, other symptoms may be observed, such as flushing, palpitation, lacrimation, rhinorrhea, urticaria, weakness, nausea or vomiting, substernal oppression, asthma and shock. Death rarely occurs. Wide variations in the severity of the above mentioned symptoms may be observed.

It is believed that this phenomenon represents an acquired sensitivity due to protein in the liver extract, a tissue reaction to histamine or the presence of a so-called *H* substance.

Efforts to combat sensitivity have been successful. The oral use of histaminase¹³ the use of antigen *H*¹⁴ to cause neutralization of histamine and desensitization of the patient by the use of gradually increasing doses of the diluted liver extract have all been successful.

A remarkable and unexplained fact is that some patients have a sensitization reaction on one occasion only. It may not recur despite the fact that treatment has not been altered.¹⁵

The opinion has been expressed that the brand of liver employed for parenteral administration has nothing to do with the incidence of sensitivity, but this is debatable

Bauer and co-workers have shown that preparations extracted from pork liver were definitely more prone to give allergic reactions than those obtained from beef liver Fourteen cases are cited in which patients reacting to pork extracts were maintained satisfactorily on extracts of beef liver

Intracutaneous tests of diluted extract are performed by many physicians in the belief that this will determine whether there is a latent sensitivity in the patient that will preclude the use of that particular preparation Actually, the skin reaction may often be positive in such tests, yet the patient may tolerate well therapeutic doses of the same extract

Carrier and Koelsche have combined desensitization to liver extract with the administration of antihistamine drugs Their method has afforded complete desensitization within a period of hours

For practical purposes, sensitivity to parenterally administered liver should be kept in mind, but the consciousness of such a possibility should not prevent the physician from using preparations which for twenty years have been the foundation for successful therapy in pernicious anemia

Measurement of Potency of Liver Preparations.—The active substance in liver that is responsible for the therapeutic response has not been identified chemically Cohn and co-workers found that the active substance was not precipitated with liver proteins, that it was water soluble but that it could be precipitated by 95 per cent alcohol This is the so-called fraction G of Cohn and was originally used orally, but soon came to be used parenterally From this, the more concentrated preparations for parenteral use were made

To date, no satisfactory methods of assay for determining the potency of liver preparations have been discovered Consequently, preparations effective in pernicious anemia must be standardized in patients in relapse To insure production and sale of potent preparations, the U S P Anti-anemia Preparations Advisory Board has been established to pass on all commercial products claimed to be effective in the treat-

ment of pernicious anemia. A "unit" has been adopted to express the amount of active substance which, when given orally or parenterally each day to patients with pernicious anemia in relapse will produce a satisfactory reticulocyte, erythrocyte and hemoglobin response.

While this measurement has been accepted generally, it has certain disadvantages. First, the amount of potent material producing a satisfactory hematologic response in one patient may not give the same result in another. Secondly, the hematologic response may not be accompanied by improvement in neurologic or gastro-intestinal symptoms. Also, the units of one preparation may vary considerably from those of another. This is a reason why a physician should become familiar with one. Units for oral administration cannot be used interchangeably with units to be given parenterally.

There are many preparations for oral administration available in the form of dry powder or in solution. Also stomach (ventriculin) or stomach-liver (extralin) preparations are on the market. Liver extracts for parenteral use, however, are to be preferred.

Liver extracts for parenteral administration vary in strength from 1 unit per 10 cc. to 15 units per 1 cc. the latter being the most potent allowed by the Advisory Board. All are given intramuscularly.

Program of Therapy with Liver Extracts —While routine procedures should not be employed to the exclusion of the patient's individual needs, certain generalities relating to therapy may be made.

We prefer the more highly refined extracts of liver (15 units per cubic centimeter) for parenteral administration. In patients with mild or moderate degrees of anemia in whom manifestations of involvement of the nervous system are absent an initial dose of from 15 to 45 units is given. Thereafter 15 units is administered twice weekly until the blood picture has been restored to normal. In patients with severe degrees of anemia who do not have evidence of involvement of the nervous system, somewhat larger doses are given. Forty five units is administered as an initial dose and repeated two days later. Thereafter, 15 units is given every

second or third day until blood values have been restored to normal. While maintenance therapy also must be individualized in each case, most patients who do not have involvement of the nervous system can be maintained satisfactorily on 15 units administered once every two to three weeks. Elderly patients or patients having acute or chronic debilitating diseases unrelated to the pernicious anemia may require somewhat larger or more frequent injections of liver extract. Moreover, patients with pernicious anemia, whether in relapse or remission, who are to be subjected to major operative procedures should be given relatively large doses of liver extract parenterally prior to operation.

The necessity for large doses of liver extract is especially great in cases in which neurologic manifestations are presented. In such cases, vigorous and persistent treatment with doses of injectable liver extract greatly in excess of the level necessary for the induction of hematologic remission must be given. It is common knowledge that progression of neurologic symptoms and signs may occur despite the fact that treatment may have been sufficiently adequate to restore blood values to normal. On the other hand, progression of neurologic manifestations not only may be arrested, but also in some patients improvement may be observed if large doses of liver extract are employed over a period of many months. Since the administration of excessive quantities of liver extract has no deleterious effects on the patient, it is far better to err on the side of administering too much than too little. As a general rule, we give 45 units daily for three consecutive days. This is followed by the administration of 15 units every second day until normal blood values have been restored. Then 30 units weekly is administered for six months or longer, followed by the administration of 15 to 30 units weekly for an additional period of twelve to eighteen months. At the end of this period, when there no longer can be hope for further improvement in neurologic manifestations, maintenance doses only slightly in excess of those given patients who have not had involvement of the nervous system may be employed.

The extent of benefit which may be expected is inversely related to the duration of involvement of the nervous system.

noted at the time therapy was first instituted. The greatest degree of improvement in neurologic manifestations occurs during the first few months of treatment, but continued improvement may occur over an additional period of eighteen to twenty four months. Instruction in co-ordinating exercises for the lower extremities, designed to re-educate patients in the use of the involved limbs, is an important adjunct to liver therapy which should not be neglected. Adherence to such a program, if followed by periodic clinical and hematologic evaluations, not only will prevent further damage to the nervous system, but also will maintain any degree of improvement that has been obtained.⁶

The administration of dilute hydrochloric acid as a routine procedure to patients having pernicious anemia is unnecessary. At times, if gastro-intestinal symptoms persist even after adequate liver therapy, a few cubic centimeters of dilute hydrochloric acid in water or fruit juice taken with meals gives prompt relief.⁶

Transfusions of whole blood rarely are necessary except in cases in which the anemia is so severe that there is evidence of circulatory collapse. When transfusions are given to the severely anemic patient they should be given very slowly to avoid congestive heart failure.⁷

DEVELOPMENT OF PTEROYLGLUTAMIC (FOLIC) ACID AND RELATED SUBSTANCES AS THERAPEUTIC AGENTS

In November, 1945, the first report on the effect of pteroylglutamic (folic) acid on macrocytic anemias in man was published.⁸ In the short period since then, voluminous literature has developed on the hematologic remissions observed when this substance is administered to patients with Addisonian pernicious anemia and related types of macrocytic anemia.^{9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100} It soon became apparent that in spite of the satisfactory hematologic response, neurologic manifestations were not arrested^{34, 37, 71, 72} and the supposition that pteroylglutamic acid might even precipitate neurologic relapse has been advanced recently by several authors.^{29, 30} Because of these facts the enthusiasm which greeted this new hematopoietic agent has been replaced by warnings regarding its use.³¹

While the advisability of the clinical use of folic acid is doubtful in view of present-day knowledge, the extensive work by various investigators that led to its discovery and synthesis is of academic interest. There are several excellent reviews relating to the discovery and biologic effects of this substance, studies that led eventually to the use of folic acid as a therapeutic agent in the macrocytic anemias.^{4,7,48,59} The reader is referred to these publications for details as it is not within the confines of this paper to do more than mention briefly the important steps not related to therapy.

Wills Factor.—As a result of the early work of Minot, Castle and their associates, it eventually became apparent that macrocytic anemias closely resembling pernicious anemia but occurring in pregnancy and nutritional deficiencies did not respond to the refined preparations of liver in the same manner as did classical Addisonian pernicious anemia. Wills and Evans postulated the presence of a new hemopoietic factor in crude liver and autolyzed yeast as being the reason that these preparations were successful in treatment of nutritional macrocytic anemia occurring in the tropics. Purified and concentrated liver extracts had not been effective in inducing remissions in this condition. It was then found that large doses of yeast alone, whether autolyzed or nonautolyzed (brewers' yeast) would, in some cases of pernicious anemia, produce a hematologic response. Watson and Castle showed that liver therapy by the oral route was effective in some cases of nutritional macrocytic anemia of pregnancy when therapy by the parenteral route was unsuccessful. Since the variation in therapeutic response to purified and crude liver was first noted by Wills, the effective principle in crude liver extracts and in autolyzed yeast has been designated the "Wills factor."⁷³ Whatever this factor is, it clearly is not identical with the antianemic principle found in liver which is effective in pernicious anemia. It is not thought to be an extrinsic factor for its antianemic effect is not related to the presence of free hydrochloric acid in gastric juice. It is regarded as probably a member of the vitamin B complex. With the demonstration by many investigators of the response of pernicious anemia and other macrocytic anemias to pteroylglutamic (folic)

acid,^{20, 21 27 70, 71} it seems probable that the activity of crude liver and yeast in the instances cited is due to their content of pteroylglutamic acid in free or conjugated form. However, this is just one link in the chain of investigations relating to this phase of the problem.

Vitamin M—In 1935 Day and associates²² produced a condition in monkeys characterized by severe anemia, leukopenia, ulceration of the gums and diarrhea when the monkeys were fed a diet deficient in vitamin G (B_{12}). The addition of brewers' yeast to the diet prevented the development of this deficiency. The effective substance in brewers' yeast was called "vitamin M."²³

Ten years later Day showed that purified *Lactobacillus casei* factor (pteroylglutamic acid) effectively induced remissions in monkeys in which the deficiency state had been produced.²⁴ Hence, another link had been added to the chain of investigations relating to folic acid.

Vitamin B₁₂—Hogan and Parrott produced a dietary deficiency in chicks which was characterized by stunted growth, incomplete feathering and macrocytic anemias. Remissions were induced by additions to the diet of an unknown substance called "vitamin B₁₂." Pfiffner and associates later isolated the antianemic factor from the liver²⁵ and eventually demonstrated that it was identical with pteroylglutamic (folic) acid.²⁶

Lactobacillus casei Factor—In 1940 Snell and Peterson showed that there was present both in yeast and in liver an unknown factor essential to the growth of one of the lactic acid bacteria. Since their test organism was *Lactobacillus casei*, this factor became known by the organism whose growth it controlled.

In 1941 a group of investigators found this factor present not only in yeast and liver, but also in spinach and in grasses. They were able to obtain extracts of it from these sources.²⁷ In addition to being essential to the growth of *Lactobacillus casei*, it was also found to be essential to the growth of *Streptococcus faecalis* R. It was then shown that both of these organisms can be used in bio-assays for determining the amount of effective substance in various foods and in

body fluids Because of the high concentration of the substance in spinach, the term "folic acid" was suggested.^{26,51}

Pteroylglutamic Acid.—Eventually it became evident that *Lactobacillus casei* factor, vitamin M, vitamin B₉, and possibly Wills factor were related and might even be identical In 1943 *Lactobacillus casei* factor was obtained in crystalline form from the liver⁵⁶ and later synthesis of this substance was announced ² "Pteroylglutamic acid" was suggested as a term for the synthetic agent,¹⁹ although "folic acid" is still commonly used ⁵¹

Pteroylglutamic acid is a bright yellow substance that is only very slightly soluble in water, while its sodium salt is fairly soluble It is destroyed rapidly by heating with dilute mineral acids, or by exposing a solution of it to sunlight Pharmacologically, it is nonirritating when injected intracutaneously, it does not affect the level of sugar in the blood and it does not affect respiration Animal experiments showed a very low toxicity and almost complete absence of side reactions,³⁸ however, in view of recent reports^{39,58} on the probability of its deleterious effect on the central nervous system in addisonian pernicious anemia, one cannot safely say that it is without toxic effect in man

Conjugates of Pteroylglutamic (Folic) Acid.—Hutchings and his associates isolated a compound which was obtained from a fermentation product of a culture of *Corynebacterium* Since it was found active for *Lactobacillus casei* growth, it was termed "fermentation *Lactobacillus casei* factor" It was found to be pteroyltriglutamic acid chemically, a conjugate of the free acid It was also shown that a conjugate of vitamin B₉ consisted of six molecules of glutamic acid in a peptide linkage ⁵⁵

Other series of compounds containing several molecules of glutamic acid were isolated from yeast Pteroylheptaglutamic acid, called the "folic acid conjugate," is found most commonly in foods ⁵⁴

Physiology of Pteroylglutamic (Folic) Acid as a Therapeutic Agent.—Bio-assay of foods and body fluids for pteroylglutamic acid or its related conjugates was made by turbidimetric methods, *Lactobacillus casei* or *Streptococcus*

lactis R being used as test organisms. While only roughly accurate as a means for quantitative measurement, such methods were considered sufficiently precise for investigational use. The heptapeptid form, as stated previously, is most commonly found in foods, since it is relatively inactive as a growth-promoting factor, it must be hydrolyzed within the body to the simpler active free form, pteroylglutamic acid. Some investigators have used the enzyme, taka diastase, while others have used alkaline or acid hydrolysis to disrupt the peptid linkage, liberating free folic acid.⁹ One group of investigators demonstrated that in a water extract of hog kidney there existed the enzyme, vitamin B₁₂ conjugase, which would liberate pteroylglutamic acid from its conjugated form, the vitamin B₁₂ conjugate (pteroylheptaglutamic acid).¹⁰ While various species of animals utilize this conjugate, it was thought that in the gastro-intestinal tract of man, enzymes in the form of conjugases were present to convert the heptaglutamates contained in foods to the simpler form, pteroylglutamic acid.¹¹

Foods have been classified as to their content of folic acid by use of turbidimetric assays.¹² Liver, kidney and fresh green leafy vegetables, such as spinach and cauliflower, are rich in folic acid, while beef and dry breakfast cereals prepared from wheat contain smaller amounts. Root vegetables, tomatoes, cucumbers, bananas, pork, lamb, cheese and milk contain relatively little folic acid. It is of interest that storage at room temperature causes great loss of folic acid, while refrigeration is quite effective in the preservation of this substance.

Metabolism of Conjugated Forms of Folic Acid —
After the ingestion of foods, the cleavage of the conjugated forms of pteroylglutamic acid by conjugase is limited by the presence of a substance called "conjugase inhibitor."¹³ Varying amounts of this substance are found in yeast, vegetables and other sources of folic acid. The importance of this inhibitory substance is readily seen when the metabolism of folic acid in normal people is compared to the metabolism of it in patients having pernicious anemia.

An estimate of a patient's ability to release this vitamin from its conjugated form has been made on the basis of the

urinary excretion of the free material after oral administration of the conjugate. It was thought that the excretion of folic acid in the free state after administration of the conjugate depended on four factors, providing renal function was normal⁷, namely, (1) liberation of the free vitamin from the conjugate, (2) its absorption from the gastro-intestinal tract, (3) the extent of tissue deficit for the vitamin and (4) the presence and functional status of tissue enzyme systems essential to the utilization of pteroylglutamic acid.

In normal subjects given pteroylglutamic acid, excretion values for the free and conjugated forms showed, if anything, a dependence on the presence of some outside source of conjugase inhibitor. In other words, a normal subject could take either the pure free vitamin or the conjugate with all of the conjugase inhibitor removed and yet show similar levels of the free vitamin in the urine. When, however, conjugase inhibitor was given at the same time as the conjugate, the urine showed a lower content of pteroylglutamic acid.⁶⁸

Similar studies were carried out on a group of patients with pernicious anemia (9 in relapse and 3 in remission).⁷ When patients were given a normal diet or when relatively large amounts of conjugate plus conjugase inhibitor were added, it was found that those with pernicious anemia in remission induced by liver therapy excreted pteroylglutamic acid in amounts equivalent to normal subjects. Patients in relapse, however, excreted less pteroylglutamic acid than did normal subjects, even though their diets included additional amounts of free folic acid or the yeast concentrate that had been incubated with the enzyme to liberate the free vitamin. Conjugated forms rich in conjugase inhibitor fed to patients in relapse also failed to cause an increase in excretion of pteroylglutamic acid.

Hematopoietic responses were observed in 2 patients having pernicious anemia in relapse who were given hexaglutamyl conjugate in a yeast concentrate containing relatively little enzyme inhibitor. It was concluded that patients with pernicious anemia in relapse do not utilize properly the naturally occurring folic acid conjugate found in foods. They required folic acid in free form in order to respond.⁸

These observations give us further insight into the etiology of this disease. Bethell and co-workers⁷ pointed out that liberation of free folic acid may be affected adversely by defective intestinal conjugase activity or even aggravated by the presence of an enzyme-inhibiting substance. Moreover, the tissue deficit for free folic acid may be so great that absorption into the tissues would be sufficient to lessen excretion in the urine. Finally, the state of the body's cellular enzyme system may be disturbed and prevent the tissues from utilizing the free vitamin.

proper functioning of the conjugase system. It may be an anti-inhibitor for this system, or a substance that increases the activity of the conjugase.⁴¹

2 The most widely heralded theory recently proposed is that of a complex type of disturbance in the enzyme system or a deep-seated biochemical derangement of the entire body.^{7,41,59} Certainly, the protean manifestations of pernicious anemia, including disturbances in the gastro-intestinal and nervous systems, imply that the derangement of metabolism is far more widespread than is the derangement involving the hematopoietic system alone. That this state constitutes more than just an inability to utilize the conjugates of pteroylglutamic acid is highly suggestive. It is of great interest that patients with pernicious anemia in whom remissions have been induced are capable of liberating free folic acid from conjugates.

3 Little actually is known as to why pteroylglutamic acid acts as it does in stimulating megaloblastic maturation in the bone marrow. Spies and his associates^{32,65} have demonstrated the antianemic properties of 5-methyl uracil (thymine), a normal constituent of the body cell which is not to be confused with thiamine (vitamin B₁).^{4,32,65} Thymine, which is part of the nucleic acid molecule, probably plays an important role in cellular metabolism. It has been shown that in large doses thymine has antianemic properties and can produce hematologic remissions in pernicious anemia. It has been suggested that pteroylglutamic acid may act as an enzyme or co-enzyme in the synthesis of thymine and in this way its hematopoietic action is effected. From a practical viewpoint, thymine has never been used clinically, since enormous doses approximating 1,200 times by weight the quantity of pteroylglutamic acid required are necessary to produce the same response in pernicious anemia.

4 Pteroylglutamic acid also has been thought to play a part in nitrogen metabolism. This was suggested by Daft after animal experimentation.

With the background afforded by these observations, one can view the clinical use of folic acid with better understanding

PTEROYLGLUTAMIC (FOLIC) ACID THERAPY IN PERNICIOUS ANEMIA

Daft showed the signs of pteroylglutamic acid deficiency in man to be anemia, leukopenia with granulocytopenia, thrombocytopenia and changes in the skin

Spies and his co-workers⁶⁶ were the first group to use free folic acid in the form of *Lactobacillus casei* factor clinically and demonstrated its effectiveness in causing remissions in 5 cases of macrocytic anemia. Free folic acid then was administered by either the oral or parenteral route to 14 patients with macrocytic anemia in relapse. These were cases of pernicious anemia in relapse, sprue and nutritional macrocytic anemia. In all except 1 case, erythrocytes returned promptly to normal in number and appearance.⁷⁰ Hence, it was concluded that regardless of the route of administration, pteroylglutamic acid had proved to be a potent therapeutic agent in certain types of macrocytic anemia in relapse.⁴⁰

Spies and his co-workers felt that subjective and objective improvement as well as the hematologic responses noted in patients with Addisonian pernicious anemia in relapse compared favorably with the improvement noted in patients with this disease who were treated with liver extract. Reticulocytosis with the peak of the response being reached between the sixth and ninth days occurred. This was followed by a gradual rise in the values for erythrocytes, hemoglobin, leukocytes and blood platelets. Regeneration in the bone marrow rapidly changed from megaloblastic to normoblastic type.⁶⁴

Because of the spectacular return of the hematologic picture to normal in pernicious anemia in relapse, pteroylglutamic acid was received enthusiastically at first. It was found to be effective orally as well as by other routes of administration. Many reports on its effectiveness soon were published. Doses ranged from as little as 1 to as much as 30 mg per day depending on individual variation. It was shown that a return in the hematologic picture to normal occurred also in many other macrocytic anemias, such as those of tropical and nontropical sprue, nutritional macrocytic anemia, pernicious anemia of pregnancy and pellagra.

Meyer was among the first to question whether pteroylglutamic acid was the answer to liver extract as a substitute for therapy in pernicious anemia. He reported that in spite of adequate dosage, that is, 15 to 50 mg a day by mouth or 20 mg a day by intramuscular injection, the reticulocyte response was submaximal when compared with that obtained with liver extract, and the hemoglobin and erythrocytes did not always return to normal values. Moreover, Meyer observed that the manifestations of peripheral neuritis or subacute combined sclerosis developed in patients with pernicious anemia when they were kept on pteroylglutamic acid therapy. In an attempt to remedy this, suboptimal doses of liver extract each day (0.5 unit) were administered concurrently with pteroylglutamic acid, the hematologic response was greater than that anticipated from adequate liver therapy alone, and neurologic manifestations showed evidence of improvement. The effect of combined pteroylglutamic acid and liver therapy could not be explained in view of the negligible amounts of free folic acid in liver extract. The inference that liver might play a role in correcting faulty cellular metabolism has been discussed previously.

NEUROLOGIC COMPLICATIONS

Meyer⁴⁸ and Hall, Watkins and Hargraves³⁷ were among the first to show that pteroylglutamic acid failed to prevent development or progression of neurologic manifestations in pernicious anemia despite the induction of hematologic remissions. In a later report,³⁶ Hall warned that pteroylglutamic acid, because of its inability to prevent the development of degenerative disease of the peripheral nerves and spinal cord in pernicious anemia, should not be substituted for extracts of liver or gastric mucosa. Of interest, too, is the observation that glossitis only temporarily abated when the patient was on treatment with free folic acid. Recurrence of glossitis was noted in some patients maintained solely on pteroylglutamic acid for a period of several months.

Soon other reports followed⁷¹⁻⁷⁴ showing excellent hematologic remissions which lasted for as long as one year but in which the development of combined system disease was not prevented even when doses up to 500 mg of folic acid per

day were given. Vilter reported that 4 out of 21 patients with pernicious anemia maintained on folic acid therapy experienced neurologic manifestations while in hematologic remission. Liver extract, however, brought about rapid improvement.

Pteroylglutamic Acid as Etiologic Agent in Neurologic Complications—Heinle and Welch²⁹ postulated that treatment with pteroylglutamic acid in pernicious anemia not only might allow neurologic manifestations to become evident, but even might precipitate them. These investigators reported a case in which neurologic relapse was unusually explosive despite a normal blood picture at the onset. In spite of forty days of adequate therapy with pteroylglutamic acid, improvement did not occur until liver extract was administered. The explosive development of the neurologic manifestations does not usually occur in combined system disease. Characteristically, combined sclerosis begins slowly and insidiously, and rarely may precede the onset of the anemia. It has been attributed to degenerative changes in the peripheral nerves and to degeneration of the posterior and lateral columns in the spinal cord. Because of the rapidity of development of neurologic manifestations in patients maintained on pteroylglutamic acid, it was thought that the hematologic and neurologic manifestations of pernicious anemia were due to the deficiency of more than one substance.

A recent report by Ross and associates has brought the problem of neurologic relapse in patients with pernicious anemia under treatment with pteroylglutamic acid to a hypo-

tered orally each day than on therapy administered parenterally at monthly intervals. These observers also noted that glossitis was not relieved completely. They also observed that normal levels of erythrocytes and hemoglobin could not always be maintained.

Of special importance was the fact that 7 out of 22 patients with pernicious anemia showed development or progression of manifestations of involvement of the nervous system, and all except 2 of these 22 patients had been kept on relatively large daily doses (10 to 15 mg. by mouth) of free folic acid.

Hemle and Welch postulated that pteroylglutamic acid exerts a deleterious effect on the nervous system and precipitates explosive neurologic manifestations. Ross and associates hypothesized that free folic acid interferes with the metabolism of *l*(+) glutamic acid, the only amino acid that has been found capable of being metabolized by nerve tissue.⁷⁴ This hypothesis was arrived at by earlier work showing that (1) *l*(+) glutamic acid could be metabolized by nerve tissue,⁶⁷ (2) brain slices could utilize glutamic acid to synthesize glutamine,⁴⁵ (3) *d*(-) glutamic acid interfered with the metabolism of nerve tissue in contrast to the metabolic activity of *l*(+) glutamic acid⁷⁴ and (4) the enzyme system in extracts of brain tissue associated with the synthesis of acetylcholine inactivated by dialysis could be reactivated by the addition of *l*(+) glutamic acid.

From these investigations it was concluded that *l*(+) glutamic acid was important in the metabolism of cells of the nervous system. It also was thought to be essential to the formation of acetylcholine, the mediator of nerve impulses.⁶³ Since glutamic acid is part of the pteroylglutamic (folic) acid molecule, it was postulated that this component of the free substance entered into competition with *l*(+) glutamic acid and interfered with nerve metabolism. This view also was held by Zimmerman and others as likely to be correct.

Davis in a recent report showed that in cases of untreated pernicious anemia the acetylcholine content of the serum was markedly elevated. The administration of pteroylglutamic acid, liver extract or ventriculin to these patients produced a decrease in the acetylcholine concentration of the blood.

2 Pteroylglutamic (folic) acid should not be used as the sole therapeutic agent in pernicious anemia

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